Effective Health Care Program

Comparative Effectiveness Review
Number 163

Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections

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Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2012-00014-I

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AHRQ Publication No. 15(16)-EHC033-EF
January 2016

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Suggested citation: McDonagh M, Peterson K, Winthrop K, Cantor A, Holzhammer B, Buckley DI. Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections. Comparative Effectiveness Review No. 163. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 15(16)-EHC033-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Leah Williams, B.S., for editorial support; Elaine Graham, M.L.S., for assistance with project management; Jessica Griffin, M.S., and Sujata Thakurta, M.P.A.:H.A., for work on the refinement phase of this project; Rebecca Holmes, M.D., M.S., for assistance with quality assessment of observational studies; and Ryan Stoner, M.A., and Laura LaLonde for data extraction and bibliographic assistance. We would also like to thank our AHRQ Task Order Officer, Elisabeth Kato, M.D., M.R.P., for her support and guidance in developing this report and our Associate Editor, Eric Bass, M.D., for his review of this report.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Interventions To Improve Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections

Structured Abstract

Objectives. To assess the comparative effectiveness of interventions for improving antibiotic use for acute respiratory tract infections (RTIs) in adults and children.

Data sources. Electronic databases (MEDLINE® from 1990 and the Cochrane Library databases from 2005 to February 2015), reference lists of included systematic reviews, and Scientific Information Packets from point-of-care test manufacturers and experts.

Review methods. Using predefined criteria, we selected studies of any intervention designed to improve antibiotic use for acute RTIs for which antibiotics are not indicated. Interventions were organized into education, communication, clinical, system-level, and multifaceted categories. We identified interventions that had evidence of reducing resistance to antibiotics, improving appropriate prescribing (i.e., concordant with guidelines), or decreasing overall prescribing of antibiotics for acute RTIs and not causing adverse consequences such as medical complications or patient dissatisfaction. The quality of included studies was rated and the strength of the evidence was assessed. Clinical and methodological heterogeneity limited quantitative analysis.

Results. Although reduction in antibiotic resistance is a major goal of these interventions, there were too few studies to assess this outcome. The few studies that attempted to assess appropriate prescribing had important limitations and lack of consistency in outcome definition and ascertainment methods across studies. Therefore, reduction in overall prescribing was the only commonly reported benefit across interventions. Actual use of antibiotics was also reported in too few studies to assess separately from prescribing. No intervention had high-strength evidence for any outcome. The best evidence, from an evidence base of 133 studies, including 88 randomized controlled trials, was for four interventions with moderate-strength evidence of improved or reduced antibiotic prescribing compared with usual care that also had low-strength evidence of not causing adverse consequences. These were clinic-based parent education (21% overall prescribing reduction; similar return visits); public patient education campaigns combined with clinician education (improved appropriate prescribing; 7% reduction in overall prescribing; similar complications and satisfaction); procalcitonin for adults (12% to 72% overall prescribing reduction; similar continuing symptoms, limited activity, missing work, adverse events or lack of efficacy, treatment failure, hospitalizations, and mortality); and electronic decision support systems (improved appropriate prescribing and 5% to 9% reduction in overall prescribing; similar complications and health care use). Additionally, public parent education campaigns had low-strength evidence of reducing overall prescribing, not increasing diagnosis of complications, and decreasing subsequent visits. Other interventions had evidence of improved or reduced prescribing, but evidence on adverse consequences was lacking (streptococcal antigen testing, rapid multiviral testing in adults), insufficient (clinician and patient education plus audit and feedback plus academic detailing), or mixed (delayed prescribing, C-reactive protein [CRP] testing, clinician communication training, communication training plus CRP testing). Interventions with evidence of no impact on antibiotic prescribing were clinic-based education for parents of children 24 months or younger with acute otitis media, point-of-care testing for

influenza or tympanometry in children, and clinician education combined with audit and feedback. Furthermore, limited evidence suggested that using adult procalcitonin algorithms in children is not effective and results in increased antibiotic prescribing.

Conclusions. The best evidence supports the use of specific education interventions for patients/parents and clinicians, procalcitonin in adults, and electronic decision support to reduce overall antibiotic prescribing (and in some cases improve appropriate prescribing) for acute RTIs without causing adverse consequences, although the reduction in prescribing varied widely. Other interventions also reduced prescribing, but evidence on adverse consequences was lacking, insufficient, or mixed. Future studies should use a complex intervention framework and better evaluate measures of appropriate prescribing, adverse consequences such as hospitalization, sustainability, resource use, and the impact of potential effect modifiers.

PROSPERO number: CRD42014010094.

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Executive Summary

Introduction

Antibiotics transformed the practice of medicine in the last half of the 20th century. With antibiotics, common infections and injuries that would previously have caused death or debility can now be effectively treated and cured. With antibiotic use, however, some bacteria can adapt, which can result in the development of antibiotic resistance, a public health problem that has grown substantially in the last several decades. In the United States, at least 2 million people acquire infections with antibiotic-resistant bacteria each year, causing approximately 23,000 deaths.[1] Although reasons for higher rates of antibiotic resistance at a population level are multifactorial, including the use of antibiotics in livestock and underdevelopment of new antibiotics, a key factor is high outpatient consumption of antibiotics.[1-3] In response to this public health problem, President Obama signed an Executive Order in September 2014 that encourages advancing development of new diagnostics, antibiotics, vaccines, and other therapeutics; strengthening surveillance of resistance; and enhancing antibiotic stewardship strategies.[4]

The problem of inappropriate antibiotic use may be biggest for uncomplicated acute respiratory tract infections (RTIs) because they account for approximately 70 percent of primary diagnoses in adults presenting for ambulatory care office visits with a chief symptom of cough.[5] Acute RTIs include acute bronchitis, acute otitis media (AOM), pharyngitis/tonsillitis, rhinitis, sinusitis, and other viral syndromes, but not community-acquired pneumonia or acute exacerbations of chronic obstructive pulmonary disease, bronchiectasis, or other chronic underlying lung diseases.[6] Despite guidelines recommending no antibiotic treatment for uncomplicated acute RTIs, the majority of outpatient antibiotic prescriptions in the United States are for acute RTIs. The National Ambulatory and National Hospital Ambulatory Medical Care Surveys found that in the period 2007−09, antibiotics were prescribed during 101 million ambulatory visits for patients aged 18 years and above annually.[7] Similarly, although the majority of bronchitis and pharyngitis is viral rather than bacterial, a 2013 report on healthy adults visiting outpatient offices and emergency departments (EDs) for acute bronchitis found that antibiotics were prescribed at 73 percent of visits from 1996 through 2010,[8] and a 2014 analysis of data from the National Ambulatory and National Hospital Ambulatory Medical Care Surveys indicated that 60 percent of children diagnosed with pharyngitis from 1997 through 2010 were prescribed antibiotics.[9]

The reasons for overuse of antibiotics for acute RTIs are numerous, diverse, and complex, with both internal and external factors, including geographic location; environment (e.g., clinic type); patient demographics (e.g., children vs. adults); availability of followup care; patient and clinician preferences, communication, and relationship; clinician specialty, knowledge, and experience; clinical inertia; peer group influence; and oversight or feedback from infectious disease experts.[10-12] Consequently, strategies to reduce antibiotic use for acute RTIs have varied targets. Strategies may target clinicians who care for patients with acute RTIs in outpatient settings, adult and/or pediatric patients with acute RTIs, the parents of pediatric patients with acute RTIs, healthy adults and/or children in the general population without a current RTI, or organizations whose attendance policies may indirectly affect the use of antibiotics (e.g., employers, school officials). Intervention strategies have also varied in the ways they are designed to change antibiotic prescribing behavior, including education, strategies to improve communication between clinicians and patients, clinical strategies such as delayed prescribing or

use of point-of-care diagnostic tests, system-level strategies such as clinician reminders or audit and feedback, or multifaceted approaches that incorporate various elements.

Interventions to improve antibiotic use are intended to achieve a variety of outcomes, including diminished antibiotic resistance, fewer adverse drug events, and decreased health care costs. However, long-term studies to evaluate these important impacts are largely yet to be done, and studies of antibiotic resistance would need to be conducted in large populations and over long time periods. In the absence of patient-centered outcomes, it has been suggested that the rate of "inappropriate" prescription of antibiotics would be the best surrogate outcome. But although a number of guidelines define when antibiotic use is warranted, defining and determining "appropriate" use for study purposes is difficult because determination of appropriateness is subjective and requires both access to adequate patient-level data and clinical knowledge. Similarly, while "prescription" and "use" are not synonymous, measuring actual use is much more difficult and resource intensive than counting prescriptions. Therefore, studies have generally evaluated the impact of interventions on overall antibiotic prescriptions, based on the understanding that for certain clinical condition, the majority of antibiotic use is unnecessary and should be reduced. The usefulness of overall prescribing as a proxy for appropriate prescribing may vary because the rate of inappropriate prescribing ranges widely, from 50 to 80 percent, based on patient, provider, and setting factors.[13,14]

A main concern with using a reduction in overall prescribing of antibiotics for RTIs as a measure of success is that it may increase the risk of undertreatment of patients for whom antibiotics would have been indicated and lead to increases in undesirable outcomes, such as hospitalization, medical complications, clinic visits, time off work and/or school, patient dissatisfaction, and longer symptom duration. In addition, the interventions may require substantial time and resources. Therefore, these negative outcomes must be assessed alongside the prescribing outcomes.

A number of existing systematic reviews and guidelines have contributed to our understanding of what works for targeted populations, interventions, or diseases.[15-22] However, because improving antibiotic use has become an increasingly urgent public health priority, there is an important need for an updated comparative effectiveness review that comprehensively addresses a broad range of interventions and populations in one review. The goal of the present systematic evidence review is to assess the comparative effectiveness of possible strategies for reducing antibiotic use in adults and children with acute RTIs. In addition to providing evidence on the benefits and potential harms of strategies, the review identifies gaps in the literature and suggestions to guide future research.

The Key Questions used to guide this report are as follows:

Key Question 1. For adults and children with an acute respiratory tract infection, what is the comparative effectiveness of particular strategies in improving the appropriate prescription or use of antibiotics compared with other strategies or standard care?

Key Question 2. For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?

Key Question 3. For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization, and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

Key Question 4. For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?

Key Question 5. For adults and children with an acute respiratory tract infection, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute respiratory tract infections (clinicians and/or patients), improved shared decisionmaking regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

Key Question 6. What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute respiratory tract infections (e.g., increased time burden on clinicians, patients, clinic staff)?

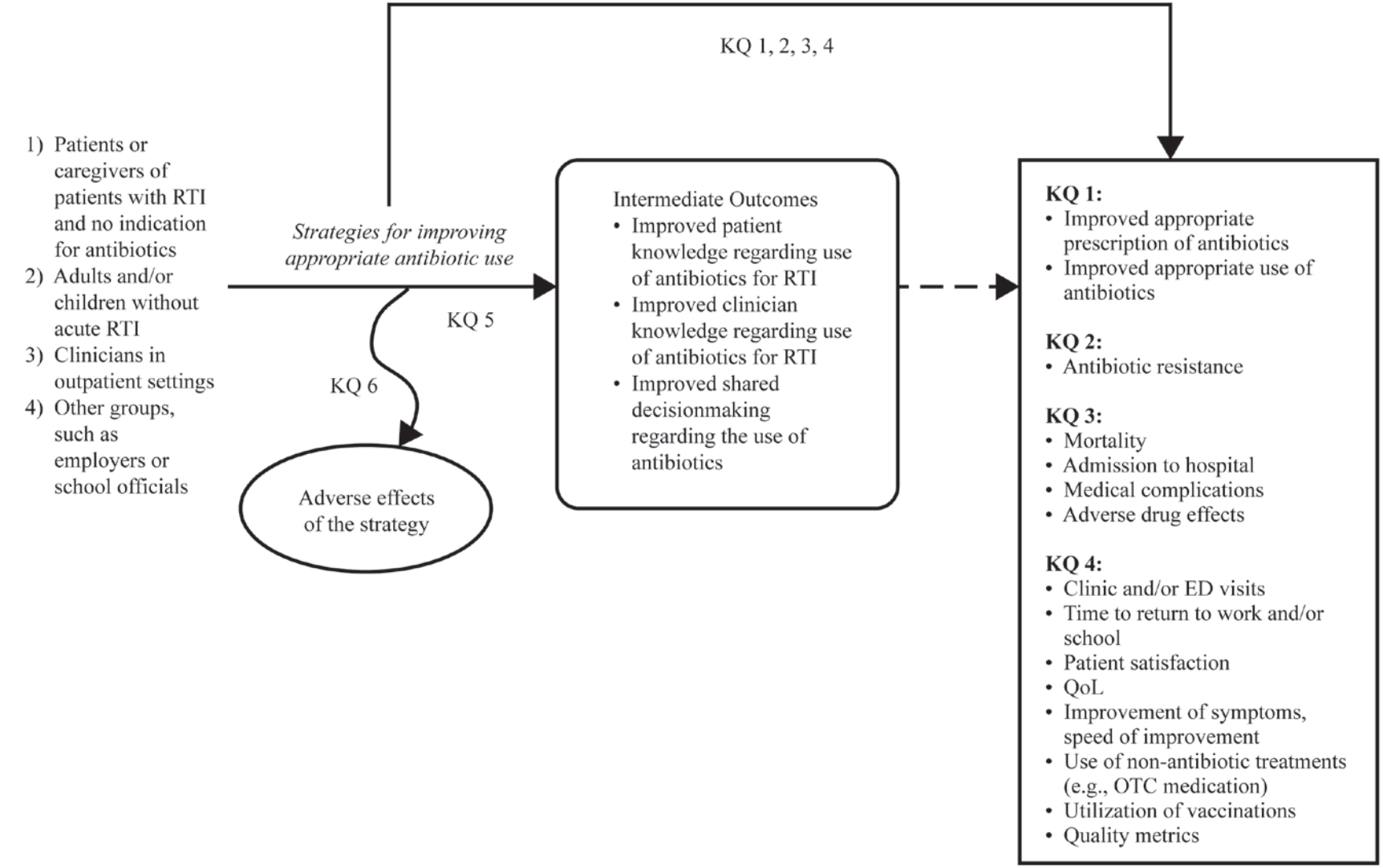
For Key Questions 1 through 4, the following subquestions were also addressed:

a. Does the comparative effectiveness of strategies differ according to how appropriateness is defined? (Key Question 1 only)
b. Does the comparative effectiveness of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, or both)?
c. Does the comparative effectiveness of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
d. Does the comparative effectiveness of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
e. Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
f. Does the comparative effectiveness differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza

epidemic, a pertussis outbreak), system-level characteristics, or whether the intervention was locally tailored?

The analytic framework below (Figure A) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis, and their relationship to the Key Questions. Specific details regarding patient population, intervention components, and outcomes are provided in the next section.

Figure A. Analytic framework for improving appropriate antibiotic use for acute respiratory tract infections



ED = emergency department; KQ = Key Question; OTC = over-the-counter; QoL = quality of life; RTI = respiratory tract infection

Methods

This Comparative Effectiveness Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[23] All methods were determined a priori. The protocol is registered with the PROSPERO international database of prospectively registered systematic reviews and is available at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010094.[24]

Literature Search Strategy

Our medical librarian searched Ovid MEDLINE® and CENTRAL from 1990 to May 14, 2014, and the Cochrane Database of Systematic Reviews from 2005 to March 2014. Additional sources included systematic review reference lists, Scientific Information Packets, and consultation with Technical Expert Panel (TEP) members.

Literature searches were updated while the draft report was posted for peer review and public comment in February 2015. Studies identified through the update searches were assessed using the same process of dual review as used for studies identified during the initial searches. Pertinent new literature meeting inclusion criteria was incorporated before the final submission of the report.

Inclusion and Exclusion Criteria

Studies were included based on the PICOTS (populations, interventions, comparators, outcomes, timing, and settings) detailed in Table A. Based on input from our TEP, and as we recognized that the 1990s marked the decade when many organizations, such as the Centers for Disease Control and Prevention, initiated formal efforts to promote appropriate antibiotic use, we restricted inclusion to studies published since 1990. Because of resource limitations, we included only studies published in English. Studies published in other languages but otherwise appearing to be eligible based on the title or English-language abstract were identified and reviewed in order to evaluate potential language bias.

Table A. Criteria for eligibility based on PICOTS framework

PICOTS	Criteria for Eligibility
Populations	Adult and pediatric patients with an acute RTI. RTIs of interest include acute bronchitis, AOM, sore throat/pharyngitis/tonsillitis, rhinitis, sinusitis, cough, and common cold.[6] Parents of pediatric patients with an acute RTI. Healthy people without a current acute RTI, who may develop an acute RTI in the future. Clinicians and others who care for patients with acute RTI in outpatient settings, including ED physicians. Groups whose attendance policies may indirectly affect the use of antibiotics, such as employers or school officials.

Table A. Criteria for eligibility based on PICOTS framework (continued)

PICOTS	Criteria for Eligibility
Interventions	Any strategy for improving appropriate antibiotic prescribing and use for acute RTI. We grouped interventions by their components into the following five categories: • Educational/behavioral interventions for clinicians, patients, or both. • Strategies to improve communication between clinicians and patients. • Clinical strategies, such as delayed prescribing of antibiotics (includes various approaches, including issuing the prescription with instructions to delay, issuing a postdated prescription, and leaving prescriptions for collection), clinical prediction rules, or use of relevant point-of-care diagnostic tests. Any point-of-care tests that are available and used in primary care settings for diagnostic purposes with the ability to provide results within a reasonable period of time were included, such as inflammatory tests (e.g., procalcitonin, CRP, white blood cell); rapid multiplex PCR tests used to rule in/out organisms (e.g., rapid strep test, influenza, RSV); and routine diagnostic tests, such as chest x ray, and blood gases, when used for determining antibiotic use. • System-level strategies, such as clinician reminders (paper based or electronic), clinician audit and feedback, financial or regulatory incentives, outpatient antimicrobial stewardship programs, and pharmacist review. • Multifaceted approaches combining one or more of the above strategies.
Comparators	Different strategies for improving appropriate use of antibiotics. Standard care without a strategy for improving appropriate use of antibiotics.
Outcomes	**Key Question 1** Increased appropriate prescription or use of antibiotics for acute RTIs. Reduced overall prescribing or use of antibiotics for acute RTIs. **Key Question 2** Antibiotic resistance. **Key Question 3** Admission to hospital. Medical complications. Adverse drug effects, including *Clostridium difficile* infections. Mortality. **Key Question 4** Clinic visits (index, return, and subsequent episodes), ED visits. Time to return to work and/or school. Patient satisfaction. Quality of life. Improvement in patient symptoms, speed of improvement. Use of nonantibiotic treatments, such as over-the-counter medications. **Key Question 5** Intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute RTI (clinician and/or patient) or improved shared decisionmaking. **Key Question 6** Adverse effects of the strategy, such as increased time burden on clinicians, sustainability of intervention, diagnostic resource use, diagnostic coding shifts.
Timing	Any duration of followup.
Setting	Outpatient care settings, including institutional settings, emergency care settings, and other settings, such as school or workplace.
Study Designs	Systematic reviews with similar scope and search dates within past 3 years. RCTs. Prospective and retrospective cohort studies, including database studies. For areas in which such direct comparative evidence is lacking, before-after studies that used methods to control for potential confounding and studies with a time-series design that evaluated temporal trends.

CRP = C-reactive protein; ED = emergency department; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; PCR = polymerase chain reaction; RCT = randomized controlled trial; RSV = respiratory syncytial virus; RTI = respiratory tract infection

Study Selection

Study selection followed AHRQ guidance for reducing bias.[25,26] Abstracts for citations identified through searches were screened for eligibility by one reviewer, with any deemed ineligible checked by a second reviewer. Full text of all citations deemed potentially eligible for inclusion by at least one reviewer was obtained for further evaluation by two reviewers, with differences in judgment on eligibility resolved through consensus or inclusion of a third party.

Data Extraction

Study characteristics and results were abstracted from included studies. One reviewer abstracted study data and a second reviewer appraised the abstractions. Intention-to-treat results were recorded if available. We considered potential effect modifiers or sources of heterogeneity, which are listed in Table B.

Table B. Potential sources of heterogeneity

Category	Sources of Heterogeneity
Populations	Type of RTI, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior RTIs, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained
Interventions	Clinician characteristics: specialty, number of years in practice, type of clinic, geographic region, and population served Diagnostic method or definition used Clinician's perception of the patient's illness severity Clinician's diagnostic certainty Local tailoring (e.g., providing intervention in languages used commonly in the local area) Accuracy of diagnostic tests
Outcomes	Appropriate prescription/use: definition of appropriateness Antibiotic resistance: data source (i.e., population vs. study sample)
Setting	Time of year; whether during a disease epidemic or outbreak period

RTI = respiratory tract infection

Quality (Risk-of-Bias) Assessment of Individual Studies

The internal validity (quality) of systematic reviews, randomized controlled trials (RCTs), and observational studies was assessed based on predefined criteria established by the Drug Effectiveness Review Project.[27] All assessments were done at the overall study level and resulted in a rating of good, fair, or poor. We used a dual rating procedure for study quality in which all studies were first rated by one reviewer and then checked by another reviewer. All disagreements were resolved using a consensus process.

Data Synthesis

We used a hierarchy-of-evidence approach that focused on the best evidence for each question, organized into the five intervention categories shown previously (Table A). We synthesized outcome data quantitatively using meta-analysis to pool outcomes where appropriate. When meta-analysis was not suitable because of significant heterogeneity in design, patient population, interventions, and outcomes, we synthesized the evidence qualitatively by grouping studies by similarity of population and/or intervention characteristics, including the sources of variation or heterogeneity listed in Table B.

For this project, one of the primary outcomes that Key Informants were interested in was improved appropriate antibiotic use. As specified in Key Question 1, we looked for studies with

outcomes on appropriate antibiotic prescribing and use. However, most studies did not measure outcomes in this way, and the few studies that attempted to assess appropriate prescribing had important limitations in outcome definition and ascertainment methods, and lack of consistency in methods across studies. Similarly, very few studies measured actual use of prescribed antibiotics, and even fewer studies reported antibiotic resistance as an outcome. This left overall prescribing as the most common outcome. In order to address the concern that reductions in overall prescribing might lead to undertreatment, we report adverse events along with overall prescribing. Although no study examined all possible adverse consequences, we considered evidence suggesting no adverse consequences (equal or lower hospitalization, equal or lower return visits, equal or higher patient/parent satisfaction) as reassuring.

To present the evidence in the most useful format for decisionmakers, we grouped the interventions into four categories based on the direction and strength of evidence for benefits (prescribing and/or resistance) and adverse consequences (e.g., reconsultations). These are—

1. Interventions with evidence of improved or reduced prescribing of antibiotics and evidence of not increasing adverse consequences: Evidence for improving appropriate antibiotic prescribing, evidence for reducing overall prescribing or antibiotic resistance (Key Questions 1 and 2), and evidence of not causing adverse consequences (Key Questions 3–6). Within this group, interventions with the highest combined level of evidence (benefits and harms) were emphasized.

2. Interventions with evidence of improved or reduced prescribing of antibiotics and no or insufficient evidence or mixed evidence on adverse consequences: Evidence for improving appropriate antibiotic prescribing, evidence for reducing overall prescribing or antibiotic resistance (Key Questions 1 and 2), and either (a) no or insufficient evidence about causing adverse consequences (Key Questions 3–6) or (b) mixed evidence on adverse consequences (some showing no impact, some showing adverse impact). In either case, this group represents interventions that require further study to make a determination on their overall effect. The two situations (a) and (b) are discussed separately, as their implications for future research differ.

3. Interventions with evidence of no effect on prescribing of antibiotics: Evidence of not improving appropriate antibiotic prescribing, overall prescribing, or antibiotic resistance (Key Questions 1 and 2), with or without evidence on adverse consequences (Key Questions 3–6).

4. Interventions with evidence of a negative effect on prescribing of antibiotics: Evidence of having a negative effect on appropriate antibiotic prescribing, overall prescribing, or antibiotic resistance (Key Questions 1 and 2), with or without evidence on adverse consequences (Key Questions 3–6).

Given the large number of interventions to consider, those with insufficient evidence are not discussed in detail in this Executive Summary.

Strength of the Body of Evidence

We used methods outlined in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" to grade strength of evidence.[25,28] After consultation with the TEP members, we prioritized the following outcomes: improved appropriate prescribing (or reduced inappropriate prescribing), overall antibiotic prescribing or use, medical complications, antibiotic resistance, adverse drug effects, admission to hospital, clinic/ED visits, patient symptoms, quality of life, and adverse effects of the intervention. Domains considered in grading the strength of evidence included study limitations, consistency, directness, precision, and reporting bias, with the body of evidence assigned a strength-of-evidence grade of high, moderate, or low.

In cases in which evidence did not exist, was sparse, or contained irreconcilable inconsistency, a grade of insufficient evidence was assigned.

Applicability

We assessed applicability by analyzing study eligibility criteria, characteristics of the enrolled population compared with the target population, characteristics of the interventions, comparators compared with care models currently in use, and clinical relevance and timing of the outcome measures.[29]

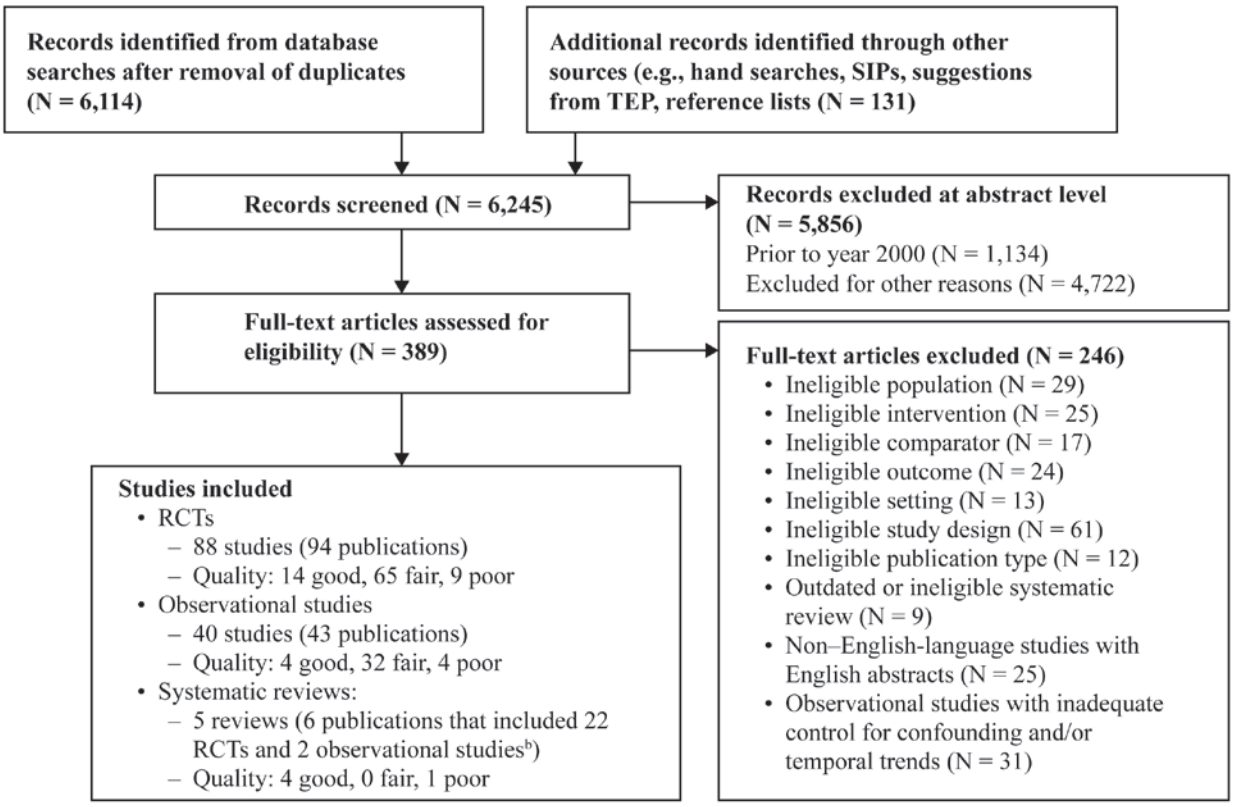
Peer Review and Public Commentary

The draft report was posted on the AHRQ Web site for 4 weeks to obtain public comments. A disposition of comments with authors' responses to the comments will be posted after publication of the final Comparative Effectiveness Review on the public Web site.

Results

The results of our searches and the selection of articles are summarized in the study flow diagram (Figure B). Our comprehensive searches resulted in 6,245 potentially relevant articles. Our review of abstracts led to retrieval and dual assessment of 389 full-text articles. Of those, a total of 133 studies (88 RCTs, 40 observational studies, and 5 systematic reviews in 143 publications) met our inclusion criteria and are included in this report.

Figure B. Results of literature searches[a]



RCT = randomized controlled trial; SIP = Scientific Information Packet; TEP = Technical Expert Panel
[a]Modified version of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart by Liberati et al., 2009.[30]
[b]RCTs and observational studies contained in included reviews are also included in counts of RCTs and observational studies.

Key Findings and Strength of Evidence

The key findings of this review are based on 128 unique RCTs and observational studies, as well as 5 reviews; most of the studies and reviews were of fair quality. Key findings are summarized in Tables C, D, and E. The factors used to determine the overall strength-of-evidence grades are summarized in Appendix J of the full report. Changes in overall prescribing were reported in all studies, while attempts to measure changes in appropriate or inappropriate prescribing were reported in nine studies (7%) and antibiotic resistance was reported in one study. In addition to the sparseness of reporting on the outcome of appropriate prescribing, the few studies that attempted to assess appropriate prescribing had important limitations in outcome definition and ascertainment methods, and lack of consistency in methods across studies. Reporting on actual patient use of antibiotics was also rare; only studies of delayed prescribing report patient self-report of filling the prescription, with use assumed.

This executive summary highlights interventions based on the direction and strength of evidence for benefits (prescribing and/or resistance) and adverse consequences (e.g., reconsultations) grouped into four categories, as described in the Methods section: (1) interventions with evidence of improved or reduced prescribing of antibiotics and evidence of not increasing adverse consequences; (2) interventions with evidence of improved or reduced prescribing of antibiotics and no, insufficient, or mixed evidence on adverse consequences; (3) interventions with evidence of no effect on prescribing of antibiotics; (4) interventions with

evidence of a negative effect on prescribing of antibiotics. Although we sought to determine whether strategies differed based on various patient, clinical, and contextual factors, this was not possible for any outcome because of the potential confounding influences of a wide variety of other factors. No intervention had high-strength evidence. Given the large number of interventions to consider, those with insufficient evidence are not discussed in the Executive Summary.

Evidence of Improved or Reduced Antibiotic Prescribing and No Increase in Adverse Consequences

Table C summarizes the evidence for these interventions. Four interventions (2 types of education programs, procalcitonin tests, and electronic decision support systems) had moderate-strength evidence for benefits and low-strength evidence for not causing adverse consequences. These interventions had the highest levels of evidence found in this report. Additionally, public education campaigns for parents had low-strength evidence for both benefits and harms.

Education Interventions

Clinic-based education interventions for parents of pediatric patients (e.g., posters, pamphlets, interactive videos) were found to reduce overall antibiotic prescribing by more than 20 percent and were not found to increase return visits for the same episode of acute RTI (N = 2 RCTs). These interventions not only feature the ability to involve the child's own clinician but also can be customized to local language and cultural needs. Evidence for the use of public education campaigns aimed at parents combined with education interventions for clinicians also shows some reduction in prescribing, although much smaller reductions of less than 10 percent (N = 5 RCTs). The evidence for this type of intervention shows reduction in inappropriate or increase in appropriate prescribing based on minimal definitions that varied by study (N = 1 RCT) and no negative impact on medical complications (N = 1 observational study) or patient satisfaction (N = 2 RCTs). Data were not available on antibiotic resistance. This evidence was moderate strength for benefits and low for harms.

With public education campaigns aimed at parents of young children (N = 2 observational studies), not combined with other interventions, prescribing for AOM was significantly reduced, while diagnosis of conditions considered potential complications was not increased and subsequent visits were decreased (N = 1 observational study). The strength of this evidence was low for all outcomes.

Point-of-Care Tests

Point-of-care tests are meant to be a rapid way to determine the likelihood that a given patient has a particular type of bacterial or viral infection, or to determine if an infection is more likely to be bacterial rather than viral. Procalcitonin was the only point-of-care test with evidence of benefit, and this benefit was restricted to adults. Use of the test in the ED or outpatient setting as a tool to help determine the need for an antibiotic resulted in reduced overall prescribing, with a fairly wide range in absolute reductions related to a wide variation in baseline prescribing (N = 1 SR of 4 RCTs). There was no negative impact on days missing work or with limited activity, symptom duration, hospitalizations, or a combined outcome of adverse events and efficacy (N = 1 RCT). Data were not available on appropriate antibiotic prescribing or on antibiotic resistance. Currently available procalcitonin tests require a number of hours, so results are not returned rapidly. This evidence was moderate strength for benefits and low for harms.

Electronic Decision Support Systems

Electronic decision support helped to reduce antibiotic prescribing for acute RTI, although the decrease was less than 10 percent and reductions were associated with higher level of use of the system (i.e., used in >50% of cases) (N = 2 RCTs). However, there was also evidence that use of these systems can improve appropriate prescribing (N = 2 RCTs) without affecting health care use or complications (N = 1 RCT). Data were not available on antibiotic resistance. This evidence was moderate strength for benefits and low for harms.

Table C. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and not causing adverse consequences

Intervention Type	Intervention (vs. Usual Care)	Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Adverse Consequences (Number of Studies) and SOE
Education	Combined patient/parent public education campaign and clinician education	Baseline: 37% to 59% (5 RCTs) Absolute: -7.3% (95% CI, 4.0 to 10.6) (5 RCTs) Relative: OR, 0.56 (95% CI, 0.36−0.87) (2 RCTs) to OR, 0.62 (95% CI, 0.54−0.75) (5 RCTs) SOE: Moderate	Reduced inappropriate prescribing— Children with pharyngitis: Baseline: 37.1% Absolute: −10.4% Relative: OR, 0.62 (95% CI, 0.54 to 0.75) Adults with acute RTIs: Baseline: 43% Absolute: −9.7% Relative: NR (2 RCTs) SOE: Low Resistance: No evidence	No difference in AOM complications (1 observational study) SOE: Low No difference in patient or parent satisfaction (2 RCTs) SOE: Low
	Clinic-based education of parents of children up to age 14 years	Control: 40.8% (1 RCT) Absolute: -21.3% (1 RCT) Relative: pooled OR, 0.39 (95% CI, 0.26 to 0.58) (2 RCTs) SOE: Moderate	No evidence	No difference in return visits (2 RCTs) SOE: Low
	Public education campaigns for parents	Children only— Baseline: 37% to 44% Absolute: NR Relative: URTI: OR, 0.75 (95% CI, 0.69 to 0.81) AOM: OR, 0.65 (95% CI, 0.59 to 0.72) Pharyngitis: OR, 0.93 (95% CI, 0.89 to 0.97) (2 observational studies) SOE: Low	No evidence	No difference in diagnosis of complications and decrease in subsequent visits (1 observational study) SOE: Low

Table C. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and not causing adverse consequences (continued)

Intervention Type	Intervention (vs. Usual Care)	Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Adverse Consequences (Number of Studies) and SOE
Point-of-Care Tests	Procalcitonin	Adults only— Baseline: 37% to 97% Absolute: -12% to -72% Relative: Acute RTI: OR, 0.14 (95% CI, 0.09 to 0.22) Acute bronchitis: OR, 0.15 (95% CI, 0.10 to 0.23) (1 SR of 4 RCTs) SOE: Moderate	No evidence	No difference in number of days of limited activity or missing work. or continuing symptoms at 28 days for URTI or LRTI in primary care (1 RCT) No difference in AEs/lack of efficacy (1 RCT) or hospitalizations (1 RCT) No difference in mortality or treatment failure at 30 days in: Acute bronchitis/URTI in primary care or ED; URTI or LRTI in primary care (5 RCTs) SOE: All low
Clinical	Electronic decision support	Systems with ≥50% use— Control group: 38% to 47% Absolute: −5% to −9% Relative: RR, 0.73 (95% CI, 0.58 to 0.92) (2 RCTs) SOE: Moderate	Improved appropriate prescribing for acute bronchitis and AOM— Baseline: 39% to 72% Absolute: −3% to −24% Relative: NR (2 RCTs) SOE: Moderate Resistance—no evidence	No difference in health care use or complications (e.g. diagnosis of pneumonia within 30 days) (1 RCT) SOE: Low

AE = adverse event; AOM = acute otitis media; CI = confidence interval; LRTI = lower respiratory tract infection; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; RTI = respiratory tract infection; SOE = strength of evidence; URTI = upper respiratory tract infection
Note: All populations are adults and children with acute RTI unless otherwise specified.

Evidence of Improved or Reduced Antibiotic Prescribing and No, Insufficient, or Mixed Evidence on Adverse Consequences

Some interventions had evidence of improving prescribing but either lacked any evidence on the impact on adverse consequences, had insufficient evidence on such outcomes, or had mixed evidence on adverse consequences (i.e., evidence of not impacting some outcomes but worsening others) (Tables D and E). This leaves important gaps in the evidence base and requires further study. For example, rapid strep testing for sore throat has moderate-strength evidence of large reductions in overall prescribing (N = 3 RCTs) and some evidence of improvement in appropriate prescribing (N = 1 RCT) compared with usual care but no evidence for other outcomes such as return visits or other adverse consequences (Table D). Rapid multiviral point-of-care testing in adults had low-strength evidence of improving prescribing outcomes compared with usual care but no evidence on adverse consequences. Combining education for patients and providers with practice profiling (audit and feedback) and academic detailing (face-to-face education specific to the provider's profile) (N = 3 observational studies) led to reduced prescribing for bronchitis (low-strength evidence), but evidence on reconsultation visits was insufficient (N = 1 observational study).

Table D. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and no or insufficient evidence on adverse consequences

Intervention (vs. Usual Care)	Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), andSOE	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Adverse Consequences (Number of Studies) and SOE
Streptococcal antigen testing (rapid strep testing)	Baseline: 58% to 72% Absolute: −20% to −52% Relative: NR (3 RCTs) SOE: Moderate	Inappropriate prescribing— Baseline: 60% Absolute: −33% Relative: NR (1 RCT) SOE: Low	NR
Rapid viral testing (multiviral PCR), adults	Baseline: NR Absolute: -7.8%; p <0.01 Relative: NR (1 RCT) SOE: Low	NR	NR
Provider and patient education + practice profiling + academic detailing	Acute bronchitis— Baseline: 21% to 88% Absolute for acute bronchitis: -24% to -26% Relative: NR (3 observational studies) SOE: Low	NR	Return clinic visits (1 observational study) SOE: Insufficient

NR = not reported; PCR = polymerase chain reaction; RCT= randomized controlled trial; RTI = respiratory tract infection; SOE = strength of evidence

Note: All populations are adults and children with acute RTI unless otherwise specified.

Some other interventions had evidence of a benefit in prescribing but also had mixed evidence on adverse consequences associated with their use (Table E). We did not attempt to weigh the various adverse consequences against the benefits of improved antibiotic prescribing because the balance depends on clinical, economic, and patient values. However, by setting the

outcomes out clearly, we hope to help decisionmakers form a judgment appropriate to their context.

Communication Training

Interventions to improve clinicians' ability to communicate with patients on decisions regarding antibiotic prescribing resulted in reductions in overall prescribing that ranged from relatively small (<10%) to fairly large (>25%) (N = 5 RCTs). Evidence on reconsultations, patient satisfaction, and hospitalizations was insufficient. Evidence on symptom improvement was conflicting, with slightly longer duration of symptoms (N = 3 RCTs) with the communication training group but better ratings of health at 2 weeks (N = 1 RCT) compared with usual care (low-strength evidence).

Delayed Prescribing

There are multiple methods of implementing delayed prescribing, as well as multiple possible comparison groups. Delayed prescribing (any method) resulted in moderate-strength evidence of large reductions in use of antibiotics compared with immediate prescribing (N = 6 RCTs). The comparison for delayed prescribing is not with usual care, in which some patients get a prescription, some do not, and some may get a delayed prescription. Hence, the reductions seen based on the delayed prescribing comparison cannot be compared with the evidence on other interventions (for which the comparison is usual care). A single study reported on patient-level antibiotic resistance, finding a lower rate with delayed prescribing. Although data were not available on appropriate antibiotic prescribing, delayed prescribing also had the benefit of reducing the incidence of antibiotic-associated diarrhea (N = 2 RCTs). While this evidence showed no impact on reconsultations (N = 4 RCTs), there was evidence of a decrease in patient satisfaction (N = 5 RCTs) and an increase in persistence of symptoms (N = 2 RCTs), adverse consequences that need to be balanced against benefits.

C-Reactive Protein (CRP)

Use of the CRP test has been shown to reduce overall prescribing for acute RTIs (N = 7 RCTs), although the absolute reductions range very widely and depend in part on the baseline prescribing rate. The evidence also indicates an increase in reconsultations within 4 weeks (N = 3 RCTs) but no effect on symptom resolution or use of chest x rays (N = 2 to 4 RCTs). Evidence on the impact on hospitalizations is less clear: five studies reported none within 30 days, and two reported higher, but not statistically significant, frequency in the CRP groups. Together, we found this to be low-strength evidence of a potential increase in risk of hospitalization within 1 month. Studies were not combinable; therefore, this evidence was low strength for a small absolute increase in risk.

Combined Interventions

There is moderate-strength evidence that clinician communication training combined with CRP testing (N = 2 RCTs) resulted in a fairly large reduction in overall prescribing (>25%) compared with usual care. There was no impact on reconsultation, diagnostic testing use, or days off work, but increased hospitalizations at 1 month (pooled unadjusted odds ratio [OR], 4.65; 95% confidence interval [CI], 1.21 to 17.87) and duration of symptoms. While these differences were statistically significant, the absolute differences were small (1.1% vs. 0.2% hospitalization

at 30 days; 5 vs. 6 days symptom duration). The reasons for even a small increased risk of hospitalization were unclear in these two trials with over 4,000 patients.

Table E. Interventions with evidence of improved or reduced prescribing for acute RTI but mixed evidence of adverse consequences

Intervention	Reduced Overall Prescribing: Baseline Prescribing Rate, Absolute Change, Relative Effect (Number of Studies), and SOE	Other Benefits (Number of Studies) and SOE	Adverse Consequences (Number of Studies) and SOE
Delayed vs. immediate prescribing	Baseline: 82% to 100% Absolute: -34% to -76% Relative: OR range, 0.00 to 0.12 (6 RCTs) SOE: Moderate	Appropriate prescribing: no evidence Reduced multidrug resistance for *S. pneumonia* strains in AOM (1 RCT) SOE: Low Reduced diarrhea in AOM (2 RCTs) SOE: Low	No difference in reconsultation (4 RCTs) SOE: Moderate Reduced satisfaction (5 RCTs) SOE: Moderate Increased persistence of moderate to severe symptoms (2 RCTs) SOE: Low
CRP vs. usual care	Baseline: 46% to 91% Absolute: -1.9% to -33.5% Relative: RR, 0.73 (95% CI, 0.60 to 0.90) (7 RCTs) SOE: Moderate	No evidence	Increased reconsultation within 4 weeks (3 RCTs) SOE: Moderate Potentially increased risk of hospitalization at 30 days: 0 events in 5 RCTs but greater in 2 RCTs (not SS) SOE: Low No impact on symptom resolution (4 RCTs) SOE: Low
Provider communication training + CRP testing vs. usual care	Baseline: 59% Absolute: −28% Relative: OR, 0.30 (95% CI, 0.26 to 0.36) (2 RCTs) SOE: Moderate	No evidence	Increased days of moderately bad symptoms (1 RCT) Potential increased risk of hospital admissions (2 RCTs) No difference in reconsultation, diagnostic testing use, or days off work (1 RCT) SOE: Low
Communication training for clinicians vs. usual care	Baseline: 27% to 79% (4 RCTs) Absolute: range, -9.2% to -26.1% Relative: RR range, 0.69 to 0.17 (5 RCTs) SOE: Moderate	No evidence	Conflicting evidence on symptom improvement: slightly longer duration of symptoms (3 RCTs) but better ratings of health at 2 weeks (1 RCT) SOE: Low

AOM = acute otitis media; CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; RTI = respiratory tract infection; SOE = strength of evidence; SS = statistically significant
Note: All populations are adults and children with acute RTI unless otherwise specified.

Evidence of No Effect on Antibiotic Prescribing

Four interventions had evidence of no impact on overall prescribing: (1) clinic-based education for parents of children 24 months of age or younger with AOM (N = 1 RCT; moderate-strength evidence); (2) clinician education combined with audit and feedback (N = 2 RCTs; low-strength evidence); (3) point-of-care testing for influenza in children (N = 1 SR of 4

RCTs; moderate-strength evidence); and (4) tympanometry point-of-care testing in children (N = 1 RCT; low-strength evidence). For influenza testing, this finding was not surprising, as clinicians were likely using the test to confirm suspected viral illness. The lack of efficacy of a parent education program for children with AOM or clinician education combined with audit and feedback was more surprising.

Evidence of a Negative Effect on Antibiotic Prescribing

Evidence in children showed that use of the adult algorithm for procalcitonin results in increased prescribing of antibiotics and a related increase in adverse events (N = 1 RCT). This suggests that procalcitonin should not be used to guide antibiotic prescribing in children without further study.

Head-to-Head Comparisons of Interventions

Single Interventions

The evidence from studies that directly compared different interventions with each other was sparse, and few studies reported outcomes other than prescribing of antibiotics. Three comparisons of single interventions found little or no difference between them.

Delayed Prescribing Strategies

Three studies comparing different methods of delaying prescribing found no difference in effect on overall antibiotic prescribing and similar rates of diarrhea or rash, duration of moderately bad symptoms, reconsultations, or satisfaction. However, reports of vomiting and abdominal pain were more frequent for giving prescriptions with instructions to delay versus leaving prescriptions for collection or requesting recontact (moderate-strength evidence).

Delayed Prescribing Versus Clinical Score

For sore throat, a study found a small reduction in overall prescriptions (<10%) and 1 fewer day of moderately bad or worse symptoms with use of a clinical score called FeverPAIN than with delayed prescribing (low-strength evidence).

Education Versus Communication Training for Clinicians

Low-strength evidence (N = 2 RCTs) showed no difference in overall or appropriate (according to guidelines) antibiotic prescribing between a clinician education intervention and a clinician communication training intervention.

Communication Training for Clinicians Versus CRP Testing

In two similar studies using a factorial design to compare communication training for clinicians, CRP testing, and the combination, there were different results for communication training alone than for CRP testing alone. A more intensive communication training program resulted in no difference in prescribing compared with CRP testing alone, while a less intensive program resulted in a lower rate of prescribing than use of CRP testing alone. There were no differences in return clinic visits or rate of improvement of symptoms.

Augmentation of Interventions (Two Versus Single Interventions)

Communication Training for Clinicians

In a trial of communication training combined with clinician education compared with education alone, there was no difference between groups in the proportion of antibiotics that were prescribed according to guidelines for acute RTI.

Point-of-Care Tests

Limited evidence on the addition of a point-of-care test to another intervention found that the combination resulted in less prescribing than the single intervention.

Rapid *Streptococcus* Antigen Testing

Moderate-strength evidence showed that the rapid strep test combined with a clinical score used as a decision rule (N = 2 RCTs) was superior to the decision rule alone in reducing overall prescribing, but no other outcomes were studied. Low-strength evidence also showed that the combination of a rapid strep test and a decision rule was superior to the decision rule alone (N = 1 RCT) in reducing overall antibiotic prescribing. Also, the combination of rapid strep testing and a clinical score was superior in reducing overall prescribing when compared with delayed prescribing (N = 1 RCT) (low-strength evidence).

C-Reactive Protein Testing

Based on two similar trials, communication training for clinicians combined with CRP testing showed a reduction in prescribing for acute RTIs compared with communication training alone (OR, 0.67; 95% CI, 0.56 to 0.78). The combined OR for hospitalization was 2.17 (95% CI, 0.85 to 5.50), indicating a potential increase with the combined intervention, but was not statistically significant. As noted previously for the comparison of the combination with usual care, the reasons for the small absolute increase in risk of hospitalization were unclear in this study of over 4,000 patients. The combination of communication training and CRP testing was not different from CRP testing alone in overall antibiotic prescribing, hospitalizations, duration of symptoms, reconsultations, days off work, or diagnostic test use. Low-strength evidence (N = 1 observational study) showed that adding CRP testing to patient and clinician education resulted in lower prescribing for rhinosinusitis, bronchitis, and pharyngitis. Low-strength evidence (N = 1 RCT) showed no difference between CRP testing combined with a clinical algorithm and the algorithm alone in overall antibiotic prescribing.

Differences in Outcomes According to Potential Moderators of Effect

Methods for Assessing Appropriate Prescribing

The methods for assessing appropriate prescribing fell into three categories: (1) ICD-9 (International Classification of Diseases, Ninth Revision) codes or diagnostic category, (2) adherence to a specific guideline's recommendations for antibiotic prescribing, and (3) duration of symptoms for pharyngitis or sinusitis. Although we sought to assess whether the definition of appropriateness affects the apparent effectiveness of interventions, this was not possible because of the potential confounding influences of a wide variety of other factors.

Intended Target of Intervention

The intended target of the interventions varied in the education interventions, in which the reductions in prescribing were greater when the target was the patient or parent and somewhat less when the target was the clinician or combined groups. Direct comparisons were not available, and the ranges in rates of reduction overlapped across the groups such that a clear pattern could not be established. However, it was clear that combining patient and clinician education did not result in clearly greater reductions. Clinical outcomes, including patient or parent satisfaction, were not significantly affected by the identity of the target. With interventions aimed at improving communication, only clinician-targeted interventions were found to have beneficial effects, although the patient-targeted evidence was very limited. Other interventions were either aimed only at clinicians (e.g., point-of-care tests) or always included both clinicians and patients (e.g., delayed prescribing).

Specific Acute Respiratory Tract Infections

The results for studies that either enrolled patients with specific acute RTIs or reported results stratified by type of RTI are presented in Table F. Interventions with mixed results by RTI type were patient education (with evidence of effectiveness for pharyngitis but not for AOM), clinician education (with evidence of effectiveness in AOM and pharyngitis but not sinusitis), combined patient and clinician education (with evidence of effectiveness in bronchitis but mixed evidence for pharyngitis and sinusitis), and the addition of clinician communication training to guideline education (which was found effective for sinusitis but not for bronchitis). Three interventions were found to have a significant effect in improving antibiotic prescribing across three RTI types: electronic decision support and two multifaceted interventions. Both involved clinician and patient education, but one added CRP testing and the other added practice profiling. We had no evidence on the effect of other patient characteristics on any outcome (i.e., nature and duration of signs and symptoms, previous medical history [e.g., frailty, comorbidity], prior RTIs, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained).

Table F. Effectiveness of interventions in improving antibiotic prescribing by type of respiratory tract infection

Intervention Category	Acute Otitis Media	Bronchitis	Pharyngitis	Sinusitis
Patient and clinician education		+	Mixed	Mixed
Patient education	-		+	
Clinician education	+		+	-
Electronic decision support	+	+	+	
Delayed prescribing	+			
CRP testing				+
Procalcitonin testing		+		
Rapid strep testing			+	
Combination of patient and provider education plus audit and feedback			a	
Combination of physician education, patient education, and audit and feedback		+	+	+
Combination of physician and patient education plus CRP test		+	+	+

Table F. Effectiveness of interventions in improving antibiotic prescribing by type of respiratory tract infection (continued)

Intervention Category	Acute Otitis Media	Bronchitis	Pharyngitis	Sinusitis
Adding clinician communication training to clinician education		-		+
Adding an educational leaflet for patients to a suggestion to delay prescription filling		+		

CRP = C-reactive protein

[a]Ineffective in children with pharyngitis.

+ means at least low-strength evidence of effectiveness; - means at least low-strength evidence of ineffectiveness; blank cells mean evidence not reported by diagnosis.

Seasonal Influences

Most of the studies were timed for the season with highest prevalence of disease, mainly winter months, and no clear pattern could be discerned in the results based on this factor. Local tailoring was typically done for educational interventions (e.g., using ethnically sensitive materials). Comparisons of no tailoring versus tailoring or between degrees or methods of tailoring were not possible because of the wide variation in the combinations of specific intervention details, population, and outcome measurement across studies.

Baseline Prescribing Rates

A key background factor may be baseline prescribing rates. Baseline prescribing rates varied extremely widely across studies (from a low of <10% to >90%). In some situations, the background prescribing rate was declining during the study period. While it is likely true that baseline prescribing rates influence the impact of interventions to reduce antibiotic prescribing, the poor reporting of this information severely limits the ability to analyze the potential impacts. Other background contextual factors—known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak) or system-level characteristics—were not studied explicitly and were reported inadequately to allow analysis.

We did not find evidence on other factors as potential effect modifiers (i.e., clinician characteristics such as specialty or number of years in practice, type of clinic organization, geographic region, population served, diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty).

Discussion

Findings in Relationship to What Is Already Known

A number of existing systematic reviews and guidelines have contributed to our understanding of what works for targeted populations, interventions, or diseases. The reviews are generally narrowly focused on specific types of interventions, but broadly they have concluded that multifaceted education interventions, clinician education, delayed prescribing, CRP, and procalcitonin testing may be effective in certain settings.[15-18,21,31-35] Our conclusions overlap with these findings but are not identical in that our results add evidence on more point-of-care tests and electronic decision support, as well as concluding that clinician education alone does not currently show benefit. Reasons for these differences include the addition of a large volume of newer evidence, the use of a formal system to grade the strength of the evidence, and the scope

of interventions considered (e.g., point-of-care tests). However, a very recent systematic review of outpatient antimicrobial stewardship programs that had a broader scope than this review (including cost outcomes, antibiotic selection outcomes, and a broader range of diagnoses) had similar findings for several interventions: education, delayed prescribing, communication training, electronic decision support, audit and feedback, and point-of-care testing.[36]

Specific interventions that have been recommended by professional organizations and societies include delayed prescribing for children with nonsevere symptoms and persistent sinusitis (American Academy of Pediatrics), patient and family education for uncomplicated acute bronchitis (Michigan Quality Improvement Consortium [MQIC] and the American College of Chest Physicians), and rapid strep testing for pharyngitis (MQIC and the Infectious Disease Society of America). Our findings expand on the evidence used to create these recommendations.

Applicability

Table G summarizes the applicability of the evidence within the elements of the PICOTS framework.

Table G. Summary of applicability

Element		Details
Population	Patients	Almost half of studies were conducted in pediatric populations (45%; mean age, 4 years), with the remainder split between adult populations (27%; mean age, 44 years) and mixed-age populations (28%; mean age, 33 years). In 62% of studies, patients had any acute RTI; in 41%, patients had pharyngitis or sore throat; in 30%, they had otitis media; and in 20−23%, they had cough or the common cold, sinusitis, or acute bronchitis.
	Clinicians	Of clinicians, 95% were in primary care (14% in emergency departments).
Intervention	Education	Education varied widely in method, duration, intensity, and local tailoring.
	Communication	Communication varied from in-person to online methods and varied in intensity and duration.
	Delayed prescribing	Methods varied widely—leaving the decision to the patient, requiring the patient to return to the clinic, or other methods.
	Point-of-care testing	CRP algorithms varied across studies. Procalcitonin algorithms were consistent across studies. Rapid viral tests included one that was multiviral, and the rest were specific for influenza. When reported, diagnostic accuracy was consistent for rapid viral and strep tests.
	System level	Computer decision support tools were somewhat variable, with some requiring active clinician access, while others used a pop-up screen.
	Multifaceted	Multifaceted interventions most often included some form of education and/or communication training combined with other interventions.
Comparators		Most often, the comparison was with usual care, but most studies of delayed prescribing compared it with immediate or no prescribing. There were few head-to-head trials of competing interventions.

Table G. Summary of applicability (continued)

Element		Details
Outcomes		Most studies focused on overall prescribing, with few studies reporting on appropriate prescribing and resistance or on the clinical consequences of reduced prescribing. Those that did used inconsistent definitions and methods.
Timeframes and settings		Of the studies, 52% were conducted in European countries, where some form of nationalized health care is common. This is an issue because the baseline or background prescribing rate varies by country, and the health care systems, cultural attitudes, and behaviors of clinicians and patients may vary enough to reduce the generalizability of the findings to a U.S. population. Most studies evaluated outcomes only over a single season. Public education campaigns are the only intervention type that evaluated outcomes over multiple seasons.

CRP = C-reactive protein, RTI = respiratory tract infection

Implications for Clinical and Policy Decisionmaking

In an effort to appropriately reduce prescribing of antibiotics for acute RTIs, clinicians and policymakers need to make choices among the relevant interventions based on the best evidence, taking into account the characteristics of the setting in which the intervention is to be applied. Although the ultimate goal is reducing antibiotic resistance while not adversely affecting clinical outcomes, antibiotic resistance was rarely studied. Although the most logical primary outcome would be changes in appropriate antibiotic use, appropriateness too was understudied. Therefore, it was necessary to consider the most widely studied, but proxy, outcome of overall prescribing to evaluate effectiveness. However, the reliability and validity of overall prescribing as a proxy for appropriate prescribing may vary because the ratio of inappropriate to appropriate prescribing can range widely based on patient, provider, and setting. Although the best evidence to date supports the use of four interventions from all categories outlined in this report (2 types of education interventions, electronic decision support, and procalcitonin), the benefit is likely to vary from situation to situation. Furthermore, these interventions have varying resource use in both implementation and maintenance, and evidence on sustainability is not available. Unfortunately, the evidence was inadequate to guide selection of the best intervention for a given setting or patient population.

Elements that could be considered in making decisions about implementation include the ability to tailor the intervention to local situations. With combined patient and clinician education programs, patient education can be simple and tailored—for example, waiting room posters featuring a letter from a local clinician. Clinician education interventions should be locally tailored and balance intensity with clinician ability and willingness to participate.

Electronic decision support systems have been shown to improve prescribing for bronchitis and AOM, and may be easily implementable in electronic medical record systems. The resources required to initiate a program and for clinicians to use such systems have not been studied, but ease of use (i.e., pop-up systems that do not require clinicians to seek out the information) may be key to ensuring adequate levels of use to result in benefit.

While rapid strep testing is the standard of care in assessing the need for antibiotics for sore throat, evidence did not support the regular use of viral testing as a way to improve prescribing of antibiotics at this time. For procalcitonin, there was agreement across algorithms in terms of thresholds for antibiotic prescribing, but the thresholds were developed for use in adults and their use in children led to increased antibiotic prescribing.

Limitations of the Review Process

Potential limitations include the exclusion of non–English-language publications, aspects of literature search strategies, and exclusion of observational studies that did not control for either potential confounding or temporal trends. However, examination of the non-English studies that had English abstracts did not identify inconsistencies in findings, suggesting that this is not a significant concern. Since no standard search terms uniformly cover all interventions and outcomes of interest, it is possible we were unable to identify all potentially relevant studies; however, our TEP members and reference lists of previously published systematic reviews were particularly useful in identifying additional citations for consideration. There was limited ability to assess potential publication and reporting bias because of the few opportunities to pool studies and the lack of availability of study protocols.

Gaps in the Evidence Base

The biggest gaps in evidence were reporting on resistance to antibiotics and use of a consistent definition of appropriate prescribing, the two most relevant outcomes for this topic. The few studies that reported appropriate prescribing had important limitations in outcome definition and ascertainment methods, and lack of consistency in methods across studies. The methods fall into three categories: ICD-9 codes or diagnostic category, adherence to a specific guideline's recommendations for antibiotic prescribing, and duration of symptoms for pharyngitis or sinusitis. None of the studies provided detailed information on how the information was obtained or assessed. Dependence on ICD-9 codes alone is a limited approach in that patient-level characteristics that may indicate the need for antibiotic therapy are not assessed. Use of a guideline to determine appropriateness of prescribing is also limited in that the determination of whether a decision adhered to the guideline is subjective and requires both access to adequate patient-level data and clinical knowledge. While the duration of symptoms beyond a suggested cutoff may be an indicator for when antibiotics are needed, this information alone is inadequate to make a precise determination.

For overall prescribing outcomes, our ability to judge the meaningfulness of the reductions was limited because of a general lack of established parameters for minimally important difference. There was also limited and inconsistent reporting on adverse clinical outcomes, hampering assessment of benefit and adverse consequences. We also could not assess how to optimize use of effective interventions because of the lack of sufficient detail on potential effect modifiers (e.g., patient, clinician, setting characteristics). Since individual interventions have been previously shown to have some benefit in reducing unnecessary antibiotic prescribing for acute RTI, the concept of multifaceted interventions holds promise for improved outcomes with greater magnitude of effect. However, the consistency of multifaceted interventions is largely unknown, and collectively they do not provide a cohesive picture of effectiveness because most studies represent a "one-off" intervention that could not be combined. In studies that measured adverse consequences, there was rarely adequate statistical power to identify statistically significant differences and no consensus about what constitutes an important difference (clinically, economically, or from the patient's perspective).

The potential for increased risk of hospitalization within 1 month of the index visit found with CRP testing, communication training, and their combination is concerning and deserves further scrutiny (Table H). The evidence of potential increased risk comes largely from three trials: a single, large (N = 4,264), fair-quality factorial-design trial of CRP testing,

communication training, or their combination conducted in clinics; a smaller (N = 431) study with similar design; and a small study of CRP testing only, conducted in EDs (N = 139). The larger multifactorial study presented an analysis considering CRP test use with or without communication training compared with usual care or communication training alone. After adjusting for potential confounders, this study found a non–statistically significant increased risk with use of CRP testing (22 vs. 8 events). An analysis of only CRP use versus only usual care was not done. The small study of only CRP testing found a similar non–statistically significant increased risk; however, in five other studies there were no hospitalizations in either group. These studies were not pooled because of clinical and methodological differences between studies.

Based on events reported in the larger study, communication training also resulted in a non–statistically significant increase in risk of hospitalization within a month. For the combination of CRP testing and communication training, reported in two similar multifactorial trials, we found a statistically significant increased risk, although this pooled estimate was unadjusted for potential confounders.

The reasons for a potential increased risk of hospitalization are unclear because the studies were not designed to examine this outcome in depth. Since the absolute numbers of events were low, the estimates are likely to be unstable and could change with additional data.

Table H. Risk of hospitalization at 1 month after index visit

Intervention Versus Usual Care	Study	Incidence	Relative Risk (95% Confidence Interval)
CRP testing	Little, 2013[37]	1% vs. 0.2%	Adjusted 2.91 (0.96 to 8.85)
	Gonzales, 2011[38]	6% vs. 3%	1.77 (0.34 to 9.30)
	Aabenhus, 2014[22]	5 studies = 0 events	Not estimable
Communication training	Little, 2013[37]	0.5% vs. 0.2%	2.35 (0.48 to 11.60)
Combination of CRP testing and communication training	Little, 2013[37] Cals, 2011[39]	1.1% vs. 0.2%	Pooled (unadjusted) 4.65 (1.21 to 17.87)

CRP = C-reactive protein, EPC = Evidence-based Practice Center

Finally, with only 45 percent of studies conducted in the United States, there may be concern about whether evidence generated in other cultures and health care systems is applicable to U.S. settings. Differences in effect were not seen where similar studies were conducted in U.S. and non-U.S. settings.

Future Research Needs

Based on the gaps and weaknesses identified through the systematic review of the literature, the following areas present an opportunity for new research to support health care decisions. All studies of interventions to improve appropriate antibiotic prescribing in acute RTIs should have the study design and reporting features identified in Table I.

Table I. Future research recommendations based on evidence gaps

Evidence Gap	Recommendation
Study design and reporting	Most studies in this area can be randomized, and in such cases, cluster randomization should be used.
	Nonrandomized studies must adhere to the best methods, particularly using methods to control for potential confounding.
	Future systematic reviews should be comparative. Several interventions are now known to improve overall antibiotic prescribing, specifically for acute RTIs, such that the questions now include how competing interventions compare with each other. All relevant and reasonable interventions that might be considered should be included.
	To ensure better reporting of important details about methods and PICOTS characteristics, we encourage increased adherence to standardized reporting guidelines, such as the TIDieR extension of CONSORT and STROBE for nonrandomized studies
Interventions and comparators	Interventions and comparators should include competing interventions from the best ones identified in this report rather than designing a new intervention each time a study is undertaken. When developing new interventions, consider evidence on what has and has not worked to date.
	Studies of procalcitonin point-of-care tests in children with acute RTIs in primary care are needed after an algorithm specific to this population has been developed.
	Studies comparing combined patient and clinician education, communication training, delayed prescribing, point-of-care tests, electronic decision support, and combined communication training and CRP testing should be undertaken. Delayed prescribing should also be compared with usual care.
	Studies of multifaceted interventions, using components of the interventions noted in this report to be effective and having adequate design and sample size, should be undertaken.
Outcome measures	The lack of consensus on how to define and measure appropriate antibiotic prescribing and use needs to be resolved. The definition needs to be clinically defensible; the ascertainment of this outcome needs to include some level of chart review. Measuring change in actual antibiotic use, rather than antibiotic prescribing only, is preferable.
	Clinical outcomes and adverse consequences of the competing interventions in addition to benefits should be measured.
	Resistance should be measured as an outcome. Because culture and sensitivity testing is rarely routinely performed in outpatient settings, we recognize that there are major practical challenges with researching resistance, including that it would require years of additional funding and long-term monitoring. However, we still recommend that, under ideal circumstances, measuring an intervention's impact on resistance would be very useful.
	Sustainability of interventions shown to be effective needs to be studied, including what happens if and when the intervention is withdrawn and effects of time and changing baseline prescribing rates.
Analysis	Background contextual factors must be reported and considered, particularly baseline prescribing rates for particular acute RTIs.
	Patient and provider characteristics should be reported more clearly and analyzed as effect modifiers.
	Methods for studying complex interventions should be applied to future research to address issues such as intervention setting characteristics; variability of interventions across studies and time, particularly multifaceted interventions; and generalizability of interventions and results.[40]
	Multifaceted interventions should be studied as systems, and issues of generalizability of the intervention system should be considered.

CONSORT = Consolidated Standards of Reporting Trials; CRP = C-reactive protein; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RTI = respiratory tract infection; STROBE = STrengthening the Reporting of OBservational studies in Epidemiology; TIDieR = Template for Intervention Description and Replication

Conclusions

The best evidence supports the use of specific education interventions for patients/parents and clinicians, procalcitonin testing in adults, and electronic decision support to reduce overall antibiotic prescribing (and in some cases, improve appropriate prescribing) without causing adverse consequences, although the reduction in prescribing varied widely. Additionally, public parent education campaigns had low-strength evidence of reducing overall prescribing, not increasing diagnosis of complications, and decreasing subsequent visits. Other interventions had evidence of improved prescribing, but evidence on adverse consequences was lacking (streptococcal antigen testing, rapid multiviral testing in adults), insufficient (clinician and patient education plus audit and feedback plus academic detailing), or mixed (delayed prescribing, CRP testing, clinician communication training, communication training plus CRP testing). Interventions with no impact on antibiotic prescribing were clinic-based education for parents of children 24 months of age or younger with AOM, point-of-care testing for influenza or tympanometry in children, and clinician education combined with audit and feedback. Furthermore, limited evidence suggested that using adult procalcitonin algorithms in children is not effective and results in increased antibiotic prescribing. Future studies should use a complex intervention framework and better evaluate measures of appropriate prescribing, adverse consequences such as hospitalization, sustainability, resource use, and the impact of potential effect modifiers.

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Introduction

Antibiotic Use and Antibiotic Resistance

Antibiotics transformed the practice of medicine in the last half of the 20th century. Penicillin was even considered by many to be a miracle drug. Beginning in the 1940s, antibiotics seemed to be the key to the inevitable elimination of infectious disease as a serious public health problem. With antibiotics, common infections and injuries that would previously have caused death or debility could now be effectively treated and cured. With antibiotic use, however, some bacteria can adapt, which can result in the development of antibiotic resistance, a public health problem which has grown substantially the last several decades. In the United States each year, at least 2 million people acquire infections with antibiotic-resistant bacteria and 23,000 people die of such infections.[1] Although reasons are multifactorial, including the use of antibiotics in livestock, a key factor known to be contributing to higher rates of antibiotic resistance at a population level is high outpatient consumption of antibiotics.[1-3] To emphasize the need to curb the rise of antibiotic resistance as a public health priority, in September 2014, President Obama signed an Executive Order that directs combative actions including advancing development of new diagnostics, antibiotics, vaccines, and other therapeutics, strengthening surveillance, and enhancing antibiotic stewardship strategies.[4]

Use of Antibiotics for Acute Respiratory Tract Infections

Acute respiratory tract infections (RTIs) account for approximately 70 percent of primary diagnoses in adults presenting for ambulatory care office visits with a chief symptom of cough.[5] Acute RTIs include acute bronchitis, acute otitis media (AOM), pharyngitis/tonsillitis, rhinitis, sinusitis, and other viral syndromes. They do not include community acquired pneumonia or acute exacerbations of chronic obstructive pulmonary disease (COPD), bronchiectasis, or other chronic underlying lung diseases.[6] Standard recommended management of acute RTIs is to focus on ruling out serious illness for which antibiotics are indicated, such as bacterial pneumonia, and providing education and symptomatic relief for uncomplicated illnesses that do not require antibiotics. Existing clinical guidelines for adults and children suggest that acute bronchitis and other acute RTIs that can be caused by either viruses or bacteria, and which are generally self-limiting, should usually not be treated with antibiotics unless certain clinical indications are present.[6]

Despite guidelines recommending no antibiotic treatment for uncomplicated acute RTIs, the majority of outpatient antibiotic prescriptions in the United States are for acute RTIs. In 2007 to 2009, the National Ambulatory and National Hospital Ambulatory Medical Care Surveys found that antibiotics were prescribed during 101 million annual ambulatory visits for patients aged 18 years and above.[7] In 2010, approximately 801 outpatient antibiotic prescriptions were dispensed per 1,000 inhabitants in the United States.[8,9] A 2013 report regarding healthy adults visiting outpatient offices and emergency departments (EDs) for acute bronchitis revealed prescriptions for antibiotics were given at 73 percent of visits between 1996 and 2010,[10] despite the fact that the majority of acute bronchitis cases are caused by viral pathogens for which antibiotics are not helpful. Similarly, A 2014 analysis of data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey indicated that 60 percent of children diagnosed with pharyngitis in the United States between 1997 and 2010 were prescribed

antibiotics,[11] despite that the fact that only about 37 percent of pharyngitis episodes are caused by bacteria. Clearly, there is a need to identify and promote strategies that can help to bring antibiotic use for RTIs in line with current evidence-based guidelines.

Strategies To Improve Appropriate Antibiotic Use

The reasons for overuse of antibiotics for acute RTIs are influenced by numerous, diverse, and complex factors, both internal and external, including geographic location, environment (i.e., clinic type, time and resources), patient demographics (i.e., children versus adults, gender, race/ethnicity), patient and/or clinician preferences, ability to obtain followup care, clinician specialty, knowledge, experience, clinical inertia, peer group influence and oversight or feedback from infectious disease experts, and provider-patient communication and relationship.[12-14] Consequently, strategies to reduce antibiotic use for acute RTIs have varied in their targets. Strategies may target *clinicians* who care for patients with acute RTIs in outpatient settings, *adult and/or pediatric patients* with acute RTIs, the *parents of pediatric patients* with acute RTIs, *healthy adults and/or children* in the general population without a current RTI, or *groups whose attendance policies may indirectly affect the use of antibiotics* (e.g., employers, school officials).

Interventions may also fall into any of several categories based on their approach. *Educational strategies* include educating clinicians about current treatment guidelines or providing information to patients or parents of patients about why antibiotic treatment is not recommended. *Strategies to improve communication* between clinicians and patients include interventions designed to improve shared decisionmaking around use of antibiotics for acute RTIs. *Clinical strategies* include delayed prescribing of antibiotics or use of point-of-care diagnostic tests (e.g., rapid strep). *System level strategies* include clinician reminders (paper-based or electronic), clinician audit and feedback, and financial or regulatory incentives for clinicians or patients. Furthermore, *multifaceted* approaches may include numerous elements of one or more of the aforementioned strategies.

Measuring Effectiveness of Strategies To Improve Appropriate Antibiotic Use

The primary goal of improving appropriate antibiotic use is to slow the evolution of antibiotic resistance. Unfortunately, measuring this outcome accurately would require large populations and long time periods, and these types of studies are largely unavailable.

Another potential benefit of reducing overall antibiotic prescriptions is the reduced exposure of patients to potential adverse side effects. Recent studies reported in the news have drawn attention to potential adverse effects of antibiotics beyond those more established side effects such as allergic reactions or gastrointestinal disruption. One such report indicated that children with four or more courses of broad-spectrum antibiotics in their first 2 years of life were more likely to be obese later in childhood.[18] Another recent report discussed evidence that certain antibiotics might be associated with increased risks of death and serious cardiac arrhythmias during standard treatment durations.[19] The cost to patients and the healthcare system of unnecessary antibiotics should also be considered. However these other important secondary goals, like antibiotic resistance, are understudied. Therefore it is necessary to consider intermediate outcomes to evaluate the effectiveness of interventions.

The most logical intermediate outcome would be changes in appropriate antibiotic use. However, although guidelines suggest when antibiotic use is warranted, defining and determining "appropriate" use for study purposes is often difficult because it is subjective and requires both access to adequate patient-level data and clinical knowledge. For these and other reasons, the effectiveness of various interventions on antibiotic overuse has generally evaluated the impact of interventions upon overall antibiotic use, based on the understanding that for certain clinical conditions the majority of antibiotic use is unnecessary. For example, studies find that half or more of antibiotic prescriptions for acute RTIs are not necessary.[15-17] Accordingly, measures of overall change in antibiotic prescription use in such conditions are a relevant proxy for changes in appropriate use. Similarly, while "prescription" and "use" are not synonymous, measuring actual use is much more difficult and resource intensive than counting prescriptions. The usefulness of overall prescribing as a proxy for appropriate prescribing may vary because the ratio of inappropriate to appropriate prescribing can range so widely based on patient, provider and setting factors. For example, one study found a rate of 80 percent inappropriate prescribing of antibiotics for acute RTI,[16] suggesting overall prescribing is a fairly good proxy for appropriate prescribing, while another study that reported 50 percent inappropriate prescribing suggests a much lower level of confidence in the proxy measure.[17] Nevertheless, it is the most widely studied outcome for these interventions.

A main concern with reducing overall outpatient use of antibiotics for RTIs is that it would increase the risk of under-treatment of patients for whom antibiotics would have been indicated and lead to increases in undesirable outcomes such as hospitalization, medical complications, clinic visits, time off work and/or school, and longer symptom duration. Depending on patients' expectations, patient satisfaction may also be affected. The interventions themselves also may require substantial time and resources. Therefore, occurrence of these negative outcomes must be weighed against any reduction in antibiotic overuse that might be associated with a particular intervention.

As numerous patient, clinician, and setting factors may modify the comparative effectiveness of interventions to improve appropriate antibiotic use (e.g., type of RTI, patient demographics, clinician specialty, type of clinic, geographic location, etc.), a review of the evidence should seek to clarify whether there are particular subpopulations that are more or less likely to benefit.

Existing Systematic Reviews and Guidelines Addressing Antibiotic Use for Acute Respiratory Tract Infections

There are a number of existing systematic reviews and guidelines that have contributed to our understanding of what works for targeted populations, interventions, or diseases.[20-27] The most comprehensive review to date, a 2006 technical review by Agency for Healthcare Research and Quality (AHRQ), entitled "Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies Volume 4—Antibiotic Prescribing Behavior" concluded that some quality improvement strategies may be moderately effective in reducing inappropriate antibiotic prescription. While no single strategy is clearly superior, the report concludes that clinician education and delayed prescribing may be more effective in certain settings and that interventions targeting prescribing for all acute RTIs may be more effective than those that target a single type of RTI. However, because improving antibiotic prescribing has become an even more urgent public health priority, there is an important need for an updated comparative effectiveness review that comprehensively addresses a broad range of populations and

interventions. Therefore, the goal of the present systematic evidence review is to assess the comparative effectiveness of a breadth of possible strategies for reducing antibiotic use when not indicated for acute RTIs in adults and children. In addition to providing evidence on the benefits and potential harms of strategies, the review identifies gaps in the literature and suggestions to guide future research.

Scope and Key Questions

The Key Questions and analytic framework used to guide this report are shown below. The analytic framework (Figure 1) illustrates the scope of this review, including the target population, interventions, comparison, and outcomes that were examined in this review.

Key Question 1. For adults and children with acute respiratory tract infection, what is the comparative effectiveness of particular strategies in improving the appropriate prescription or use of antibiotics compared with other strategies or standard care?

a. Does the comparative effectiveness of strategies differ according to how appropriateness is defined?
b. Does the comparative effectiveness of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
c. Does the comparative effectiveness of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
d. Does the comparative effectiveness of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
e. Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
f. Does the comparative effectiveness differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), system-level characteristics, or whether the intervention was locally tailored?

Key Question 2. For adults and children with acute respiratory tract infection, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?

a. Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b. Does the comparative effect of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c. Does the comparative effect of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?

d. Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e. Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), whether the intervention was locally tailored, system-level characteristics, or the source of the resistance data (i.e., population vs. study sample)?

Key Question 3. For adults and children with acute respiratory tract infection, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization, and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

a. Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b. Does the comparative effect of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c. Does the comparative effect of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
d. Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e. Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a pertussis outbreak), whether the intervention was locally tailored or system-level characteristics?

Key Question 4. For adults and children with acute respiratory tract infection, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?

a. Does the comparative effect of strategies differ according to the intended target of the strategy (i.e., clinicians, patients, and both)?
b. Does the comparative effect of strategies differ according to patient characteristics, such as type of respiratory tract infection, signs and symptoms (nature and duration), previous medical history (e.g., frailty, comorbidity), prior respiratory tract infections, prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained?
c. Does the comparative effect of strategies differ according to clinician characteristics, such as specialty, number of years in practice, type of clinic organization, geographic region, and population served?
d. Does the comparative effectiveness differ according to the diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty?
e. Does the comparative effect differ according to various background contextual factors, such as the time of year, known patterns of disease activity (e.g., an influenza epidemic, a

pertussis outbreak), whether the intervention was locally tailored or system-level characteristics?

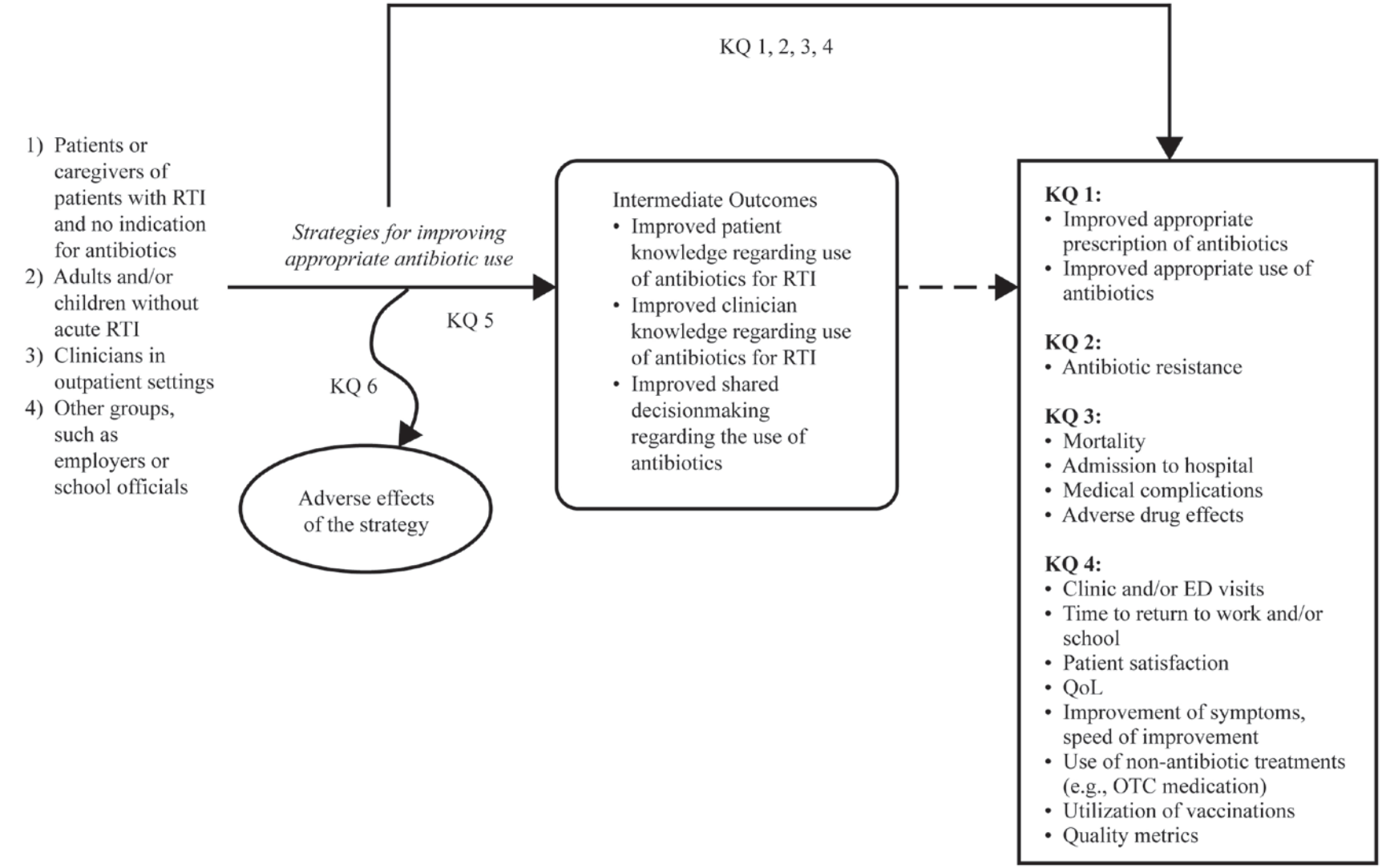
Key Question 5. For adults and children with acute respiratory tract infection, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute respiratory tract infections (clinicians and/or patients), improved shared decisionmaking regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

Key Question 6. What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute respiratory tract infections (e.g., increased time burden on clinicians, patients, clinic staff)?

Analytic Framework

The analytic framework below (Figure 1) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis and their relationship to the Key Questions.

Figure 1. Analytic framework for improving appropriate antibiotic use for acute respiratory tract infections



ED = emergency department, KQ = Key Question, OTC = over-the-counter, QoL = quality of life, RTI = respiratory tract infection

Organization of This Report

For each Key Question, results are organized into subsections for each intervention category. We arranged the subsections to match the ordering of the intervention categories as listed in the inclusion criteria. Within each intervention category subsection, evidence was further grouped by specific intervention type (i.e., delayed prescribing, specific point-of-care tests for the clinical section) and ordered based on volume of evidence (most to least).

Methods

This comparative effectiveness review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[28] The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA checklist.[29] All methods were determined a priori in the protocol, which is available at www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1913#8793.

Topic Refinement and Review Protocol

The topic was nominated by a diverse group of stakeholders, including patients, clinicians, professional societies, and insurers through an AHRQ-sponsored topic identification exercise. A panel of Key Informants gave input on the Key Questions to be examined; these Key Questions were posted on AHRQ's Effective Health Care (EHC) Web site for public comment in January 2015 for 3 weeks and revised in response to comments. We then drafted a protocol for the systematic review and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. The finalized protocol is posted on the EHC Web site at www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1913#8793. The PROSPERO registration is CRD42014010094.

Literature Search Strategy

To identify articles relevant to each Key Question, a medical librarian searched Ovid MEDLINE® In-Process & Other Non-Indexed Citations from 1990 to May 14, 2014, the Cochrane Database of Systematic Reviews (CDSR) from 2005 to March 2014, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1990 to April 2014. Search dates and exact search strings are provided in Appendix A. Gray literature was identified by searching clinical trial registries (ClinicalTrials.gov and WHO Trial Registries). We conducted hand searches for studies included in reference lists of included systematic reviews. Scientific Information Packets were solicited from relevant stakeholders (e.g., manufacturers of point-of-care tests, advocacy groups, professional societies, large healthcare organizations, etc.) through the Scientific Resource Center. A second medical librarian who provided comments to improve the strategy reviewed the search strategy.

Literature search updates were performed in December 2014 and February 2015. Studies identified were assessed using the same process of dual review as used for studies identified during the initial searches. Pertinent new literature meeting inclusion criteria was incorporated before the final submission of the report.

Inclusion and Exclusion Criteria

Studies were included based on the population, intervention, comparator, outcomes, timing, settings, and study designs (PICOTS) detailed below (Table 1). Based on input from our Technical Expert Panel (TEP), and as we recognized that the 1990s mark the decade when many organizations, such as the Centers for Disease Control and Prevention, initiated formal efforts to promote appropriate antibiotic use, the Pacific Northwest Evidence-based Practice Center (PNW

EPC) restricted inclusion to studies published since 1990. Given the existence of good systematic reviews after 2000, and information from our TEP that there are few relevant studies before 2000, we identified studies published from 1990 to 2000 through systematic reviews of the topic, with confirmation by the TEP that nothing important had been missed. Primary literature published from 2000 onward was identified through primary literature searches. Due to resource limitations, we only included studies published in English. Studies published in other languages but otherwise appearing to be eligible based on the title or English-language abstract were identified and reviewed in order to evaluate potential language bias.

Table 1. Criteria for eligibility based on PICOTS framework

PICOTS	Criteria for Eligibility
Populations	Adult and pediatric patients with an acute RTI, including acute bronchitis, AOM, sore throat/pharyngitis/tonsillitis, rhinitis, sinusitis, cough, and common cold, but not community acquired pneumonia or acute exacerbations of chronic bronchitis.[6] We did not use a specific definition of acute as a criterion for inclusion/exclusion, accepting all study definitions. Parents of pediatric patients with acute RTI. Healthy adults and/or children without a current acute RTI, who may develop an acute RTI in the future. Clinicians and others who care for patients with acute RTI in outpatient settings, including emergency room physicians. Groups whose attendance policies may indirectly affect the use of antibiotics, such as employers or school officials.
Interventions	Any strategy for improving appropriate antibiotic prescribing and use for acute RTI, including outpatient stewardship programs. We grouped interventions by their components into the following categories: Educational, behavioral and psychological interventions that target clinicians, patients, or both. Strategies to improve communication between clinicians and patients, such as those designed to improve shared decisionmaking. Clinical strategies such as delayed prescribing of antibiotics (includes various approaches with varying barriers to the patient, including issuing the prescription with instructions to delay, issuing a post-dated prescription, leaving prescriptions for collection, and requiring recontact), clinical prediction rules, use of risk assessment or diagnostic prediction, use of nonantibiotic alternatives, or use of relevant point-of-care diagnostic tests. Any point-of-care test that is available and used in primary care settings for diagnostic purposes with the ability to provide results within a reasonable period of time (e.g. during the clinic visit). Examples include inflammatory tests (e.g., procalcitonin, CRP, white blood cell, etc.), rapid multiplex PCR tests used to rule in/out organisms (e.g. rapid strep test, influenza, RSV), and routine diagnostic tests, such as chest x-ray, pulse oximetry, and blood gasses, when they are specifically evaluated as an intervention for improving antibiotic use. System level strategies such as clinician reminders (paper-based or electronic), clinician audit and feedback, financial or regulatory incentives for clinicians or patients, antimicrobial stewardship programs, and pharmacist review. Multifaceted approaches that include numerous elements of one or more of the above strategies.
Comparators	Different strategies for improving appropriate use of antibiotics for acute RTI. Standard care without a strategy for improving appropriate use of antibiotics: We use the terms usual care and standard care synonymously. Although practice probably varies considerably between settings, usual and standard practice likely includes maintaining hydration and use of decongestants, cough suppressant, etc.

Table 1. Criteria for eligibility based on PICOTS framework (continued)

PICOTS	Criteria for Eligibility
Outcomes	**Key Question 1** Increased appropriate prescription of antibiotics Increased appropriate use of antibiotics Reduced overall prescribing of antibiotics for acute RTI Reduced overall use of antibiotics for acute RTI **Key Question 2** Antibiotic resistance **Key Question 3** Admission to hospital Medical complications Adverse drug effects, including *clostridium difficile* infections Mortality **Key Question 4** Clinic visits (index, return and subsequent episodes), ED visits Time to return to work and/or school Patient satisfaction Quality of life Improvement in patient symptoms, speed of improvement Use of nonantibiotic treatments, such as over-the-counter medications **Key Question 5** Intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute RTI (clinician and/or patient), or improved shared decisionmaking **Key Question 6** Adverse effects of the strategy, such as increased time burden on clinicians, sustainability of intervention (e.g. measures of continued effectiveness over time), diagnostic resource use associated with point-of-care testing, diagnostic coding (e.g., ICD billing codes) according to desired action (prescribe/not prescribe)
Timing	Any duration of followup was eligible
Setting	Outpatient care settings including institutional settings, emergency care settings and other settings, such as school or workplace
Study Designs	Systematic Reviews with similar scope and search dates within past 3 years. RCTs Prospective and retrospective cohort studies including database studies For areas in which such direct comparative evidence is lacking, we included before-after studies that used methods to control for potential confounding and studies with a time-series design that evaluated temporal trends

CRP = C-reactive protein, ED = emergency department, ICD = international classification of disease, PCR = polymerase chain reaction, RCT = randomized controlled trial, RSV = respiratory syncytial virus, RTI = respiratory tract infection

Study Selection

Study selection followed AHRQ guidance for reducing bias.[30,31] Abstracts for citations identified through searches were screened for eligibility by one reviewer, with any deemed ineligible reviewed by a second reviewer. Full-text of all citations deemed potentially eligible for inclusion by at least one reviewer were obtained for further evaluation. Full-text articles were reviewed by two reviewers, with differences in judgment on eligibility resolved through consensus or inclusion of a third party.

Results published only in abstract form were not included because inadequate details were available for assessing quality. Protocols for RCTs were included to inform quality assessment of completed trials or to speak to the potential of future research. In general, at full-text level, studies were excluded for one or more of the following reasons: ineligible population, ineligible intervention, ineligible comparator, ineligible outcome, ineligible setting (e.g., inpatient),

ineligible study design (e.g., case report, qualitative methods), ineligible publication type (e.g. editorial, letter, narrative review), outdated or ineligible systematic review, or non-English language.

All citations were entered in an electronic database (Endnote® X7, Thomson Reuters) and screening decisions for each citation were also tracked in the database. Appendix B lists all studies included at full text, while all studies excluded at full text are listed in Appendix C.

Data Extraction

The following data were abstracted from included studies: study design, number of participants randomized or enrolled, patient and provider population criteria, intervention strategy and comparator characteristics, patient characteristics (e.g., type of RTI, signs and symptoms, duration of illness, age, ethnicity, and socioeconomic status), provider characteristics (e.g., specialty, number of years in practice, and type of clinic), background contextual factors (e.g., time of year, and patterns of disease activity), definition of appropriate antibiotic use, and results for each outcome. For studies of diagnostic tests, we also recorded funding source. One reviewer abstracted study data, and a second reviewer appraised the abstractions. Intention-to-treat results were recorded if available. Appendixes D, F, and H contain evidence tables for data abstraction of RCTs, observational studies, and systematic reviews. Studies are organized in alphabetical order by primary author name. We considered potential effect modifiers or sources of heterogeneity according to PICOTS categories:

Populations: Type of respiratory tract infection, signs and symptoms (nature and duration), when counting began for duration of symptoms, previous medical history (e.g., frailty, comorbidity), prior RTIs, and prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained

Interventions: Clinician characteristics: Specialty, number of years in practice, type of clinic organization, geographic region, and population served; diagnostic method or definition used; clinician's perception of the patient's illness severity; clinician's diagnostic certainty; local tailoring; accuracy of diagnostic tests;

Outcomes: Definition of appropriateness of antibiotic prescription or use and data source (i.e., population vs. study sample) for antibiotic resistance.

Setting: Time of year; during a disease epidemic or outbreak period.

Quality (Risk of Bias) Assessment of Individual Studies

The internal validity (quality) of systematic reviews, RCTs, and observational studies were assessed based on predefined criteria established by the Drug Effectiveness Review Project.[32] For trials, these criteria were based initially on the criteria used by the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom).[33,34] In rating the internal validity of trials, we evaluated methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; adequate reporting of dropouts, attrition, loss to followup; and the use of intention-to-treat analysis.

The internal validity of observational studies were rated based on criteria specific to these study designs: the adequacy of the patient selection process, whether there was important differential loss to followup or overall high loss to followup, the adequacy of event ascertainment, whether acceptable statistical techniques were used to minimize potential

confounding factors, and whether the duration of followup was reasonable to capture investigated events.

All assessments were done at the overall study level and resulted in a rating of good, fair, or poor. We utilized a dual rating procedure for study quality, where all studies were first rated by one reviewer and then checked by another reviewer. All disagreements were resolved using a consensus process.

Data Synthesis

Evidence tables were constructed to illustrate the study characteristics, quality ratings, and results for all included studies (Appendixes D through I). A hierarchy-of-evidence approach was used, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. High-quality systematic reviews that had a similar scope to our review were used as primary evidence where possible; where a review included all studies of an intervention, population, and outcome we summarized the findings of the review as our evidence. Where an eligible review did not include all identified studies we noted the review and its findings, but undertook a new synthesis to incorporate the newer studies not included in the review.

For assessing overall and appropriate prescribing and use, we accepted and recorded all definition and measurement methods. Particularly for appropriate prescribing outcomes, we grouped together studies that use similar definitions of appropriateness and evaluated whether the comparative effectiveness of strategies differed across categories.

Where appropriate, we synthesized outcome data quantitatively using meta-analysis to pool outcomes, with odds ratio as the principle summary measure. To determine the appropriateness of pooling outcomes (e.g., percent reduction in antibiotic prescribing or use) using meta-analysis, the quality of the studies and the heterogeneity among studies in design, population, interventions, and outcomes were considered. Data from poor-quality studies were generally excluded from the synthesis, except to undertake sensitivity analyses or to note where high risk of bias studies constitute the only evidence for an important outcome. To determine the appropriateness of meta-analysis, we considered the internal validity of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Appropriate measures were chosen based on the type of data for meta-analysis (e.g., relative risk, odds ratio). The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[35,36] Random-effects models were used to estimate pooled effects.[37] Statistical heterogeneity was explored by using subgroup analysis or meta-regression. Forest plots were used when applicable to graphically summarize the results of individual studies and of the pooled analysis.[38]

When both trial and observational studies were found for a given intervention-outcome pair, trial evidence was given more weight according to the EPC guidance on grading the strength of the evidence.[30] Sensitivity analyses were also conducted where possible to evaluate differing definitions for inappropriate antibiotic use.

Since most data was not suitable for pooling, we largely summarized the data qualitatively. Qualitative synthesis involved grouping studies by similarity of population and/or intervention characteristics, including the sources of variation or heterogeneity listed above. Studies varied in how appropriateness was defined or determined. We accepted and recorded any definition of appropriateness. For example, since it is not yet clear whether evidence for one RTI type is applicable to another RTI type or a mixed RTI population, we evaluated these bodies of evidence

separately. When definition of appropriate antibiotic use and/or prescription were provided, we grouped together studies that used similar definitions of appropriateness and categorized the different groups based on concordance (e.g., high, medium, low) with select clinical practice guidelines (e.g., American Academy of Pediatrics, American College of Clinical Pharmacy, American Academy of Family Physicians). We then evaluated whether the comparative effectiveness of strategies differed across categories.

For this project, one of the primary outcomes that Key Informants were interested in was improved appropriate antibiotic use. As described in Key Question 1, we looked for studies with outcomes on appropriate antibiotic prescribing and use. However, most studies did not measure outcomes in this way and the few studies that attempted to assess appropriate prescribing had important limitations in outcome definition and ascertainment methods and lack of consistency in methods across studies. Similarly, very few studies measured actual use of prescribed antibiotics and even fewer studies reported antibiotic resistance as an outcome. This left overall prescribing as the most common outcome. In order to address the concern that reductions in overall prescribing might lead to undertreatment, we report adverse events along with overall prescribing. Although no study examined all possible adverse consequences, we considered evidence suggesting no adverse consequences (equal or lower hospitalization, equal or lower return visits, equal or higher patient/parent satisfaction) as reassuring.

To present the evidence in the most useful format for decisionmakers, we grouped the interventions into four categories based on the direction and strength of evidence for benefits (prescribing and/or resistance) and adverse consequences (e.g. reconsultations). These are:

1. Interventions with evidence of improved or reduced prescribing of antibiotics and evidence of not increasing adverse consequences: Evidence for improving appropriate antibiotic prescribing, evidence for reducing overall prescribing or antibiotic resistance (Key Question 1 and 2), and evidence of not causing adverse consequence (Key Questions 3 – 6). Within this group, interventions with the highest combined level of evidence (benefits and harms) were emphasized.

2. Interventions with evidence of improved or reduced prescribing of antibiotics and no evidence or mixed evidence on adverse consequences: Evidence for improving appropriate antibiotic prescribing, evidence for reducing overall prescribing or antibiotic resistance (Key Question 1 and 2), and either (a) no evidence about causing adverse consequence (Key Questions 3 – 6) or (b) mixed evidence on adverse consequences (some showing no impact, some showing adverse impact). In either case, this group represents interventions that require further study to make a determination on their overall effect. The two situations (a and b) are discussed separately as the implications for future research differ.

3. Interventions with evidence of no effect on prescribing of antibiotics: Evidence of not improving appropriate antibiotic prescribing, overall prescribing or antibiotic resistance (Key Question 1 and 2) with or without evidence on adverse consequences (Key Questions 3 – 6).

4. Interventions with evidence of a negative effect on prescribing of antibiotics: Evidence of having a negative effect on appropriate antibiotic prescribing, overall prescribing or antibiotic resistance (Key Question 1 and 2) with or without evidence on adverse consequences (Key Questions 3 – 6).

Given the large number of interventions to consider, those with insufficient evidence are not discussed in detail in the Executive Summary. The evidence provided limited opportunity to examine potential publication and reporting biases, primarily because there were so few opportunities for meta-analysis and because so few study protocols were available.

Strength of the Body of Evidence

We used methods outlined in chapter 10 of the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews to grade strength of evidence, which is available from the AHRQ Effective Health Care (EHC) Web site at www.effectivehealthcare.ahrq.gov.[30,39] Outcomes selected for grading were those likely to be of considerable importance to users of the report. After consultation with the TEP members, we prioritized the following outcomes: improved appropriate prescribing (or reduced inappropriate prescribing), overall antibiotic prescribing, antibiotic resistance, medical complications, adverse drug effects, admission to hospital, clinic visits (index, return and subsequent episodes), ED visits, improvement in patient symptoms, speed of improvement, patient satisfaction, quality of life, and adverse effects of the intervention.

Domains considered in grading the strength of evidence included study limitations, consistency, directness, precision, and reporting bias. For evaluating precision, we did not assume any minimum important difference for continuous outcomes, as we are not aware of any that have been validated. So, we accepted any delta and assessed optimal information size for each delta separately. Publication bias was assessed following methods outlined in AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[30,39] Selective outcome and analysis reporting bias were assessed during individual study quality assessment, using trial registry protocols where available, and study publication methods where protocols were not available. Based on assessment of these domains, the body of evidence was assigned a strength-of-evidence grade of high, moderate, or low. In cases where evidence did not exist, was sparse, or contained irreconcilable inconsistency, a grade of insufficient evidence was assigned (see Appendix J).

Applicability

Applicability was assessed by paying special attention to study eligibility criteria, characteristics of the enrolled population in comparison to the target population, characteristics of the intervention and comparator used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. Methods used for assessing applicability are available from the AHRQ EHC Web site at www.effectivehealthcare.ahrq.gov.[40]

Peer Review and Public Commentary

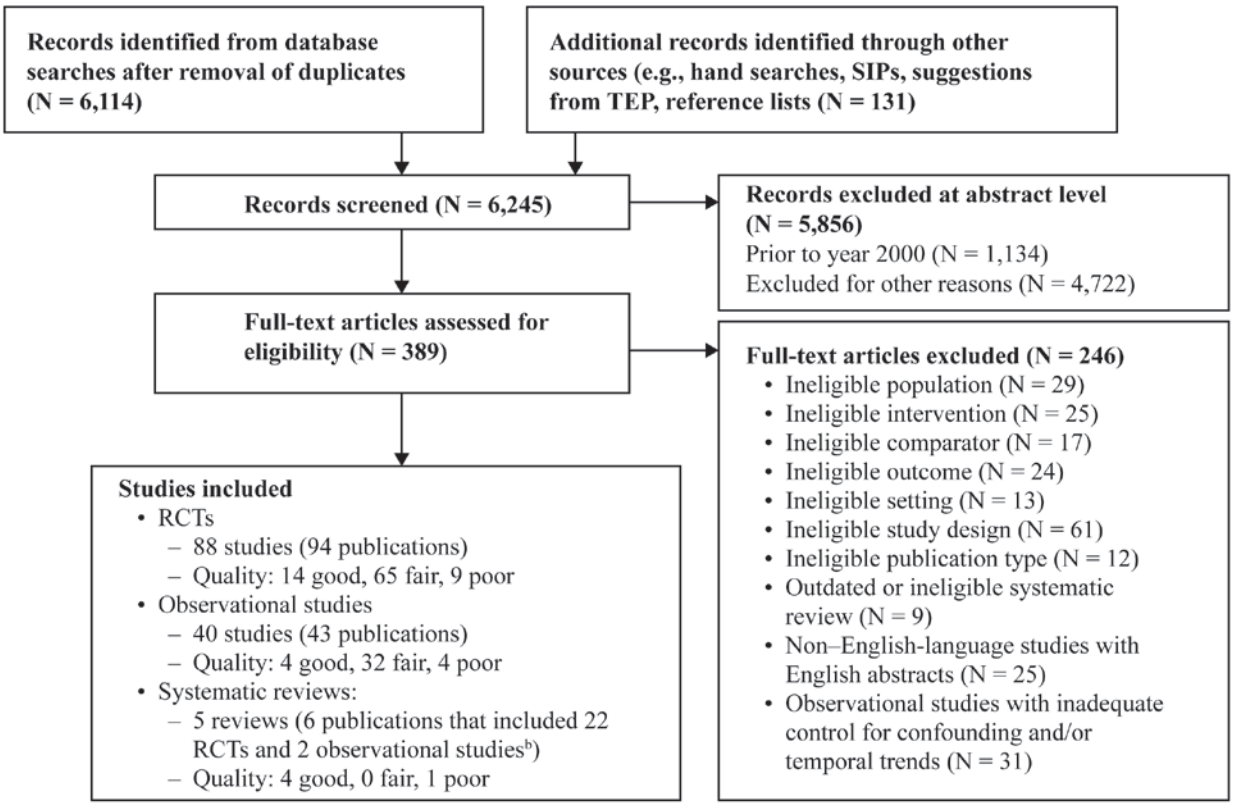
Experts in family medicine, internal medicine, primary care, point-of-care diagnostic testing, clinical pharmacy, infectious disease, epidemiology, and biostatistics provided peer review of the draft report. The AHRQ Task Order Officer and an EPC Associate Editor also provided comments and editorial review. The draft report was posted on the AHRQ Web site for 4 weeks to obtain public comments. A disposition of comments with authors' responses to the peer and public review comments will be posted after publication of the final CER on the public Web site.

Results

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of Ovid MEDLINE®, CDSR®, and CCRCT® yielded 6,114 citations. An additional 131 records were identified by manual searching (hand searches and reference lists) or were suggested by our Technical Expert Panel (TEP). Based on these sources, a total of 6,245 abstracts were screened of which 389 articles were retrieved and assessed for eligibility. Of those, a total of 133 studies (in 143 publications) including 88 randomized controlled trials (RCTs) (94 publications),[41-134] 40 observational studies (43 publications),[135-177] and five systematic reviews (6 publications)[22-27] met inclusion criteria and are included in this report. Of the 143 publications included in this report, 133 were primary study reports[22,24-27,41-54,56,58-84,86-92,95-133,135-142,144-146,148-157,159-177] and 10 were secondary publications.[23,55,57,85,93,94,134,143,147,158] Appendix B lists all included studies and Appendix C provides a complete list of articles excluded at full text with the reasons for exclusion.

Figure 2. Results of literature searches[a]



N = sample size, RCT = randomized controlled trial, SIP = scientific information packet, TEP = Technical Expert Panel

[a] Modified version of PRISMA flow chart by Liberati, 2009.[178]

[b] RCTs and observational studies contained in included reviews are also included in RCT and observational study counts.

Description of Included Studies

Table 2 summarizes the key characteristics of included studies overall and for each of the intervention categories. Educational and clinical intervention strategies were the most widely studied. The majority of studies were multisite RCTs. Most targeted broad populations of children and adults with any acute respiratory tract infection (RTI). Sore throat, pharyngitis, and tonsillitis, were generally the most common RTI types across studies, except that cough was most common in studies of communication interventions. In terms of outcomes, overall antibiotic prescription was the most widely studied, followed by return visits, symptom improvement and patient satisfaction. Changes in overall prescribing was reported in all studies, while attempts to measure changes in appropriate or inappropriate prescribing were reported in only nine studies (7%). However, actual use of antibiotics was rarely reported; the studies of delayed prescribing report patient self-report of filling the prescription and sometimes use of the prescription. Antibiotic resistance and quality of life were only reported in one study each, and some outcomes (e.g., utilization of vaccinations and quality metrics) were not reported in any studies. The proportion of studies conducted in the United States was 45 percent overall; but this ranged widely across intervention categories, from 14 percent for communication strategies to 69 percent for system-level strategies. Three of 29 (10.3%) of studies of point-of-care tests received partial funding from test manufacturers. Data abstraction tables for all included studies can be found in Appendixes D, F, and H. A complete list of abbreviations for this report can be found at the end of the report. A list of abbreviations specific to the appendixes can be found in Appendix K.

Our internal validity assessments found the majority of studies to be of fair quality. All quality ratings can be found in Appendixes E, G, and I. Our detailed analysis of results focuses on studies with good- or fair-quality ratings. For RCTs, 11 percent were rated poor quality and their main limitations included insufficient detail to assess adequacy of randomization and allocation concealment methods, imbalances at baseline in important patient characteristics, and unacceptably high and differential levels of missing data. A total of 10 percent of observational studies were also rated poor and their main limitations included biased selection and ascertainment methods and uncontrolled confounding.

Due to the heterogeneity among studies in design, population, interventions, and outcomes, there were few occasions where pooling outcomes was appropriate and data were primarily summarized qualitatively. We reported pooled analyses from existing Cochrane reviews on delayed prescribing,[22] procalcitonin,[23,24] and influenza testing.[26] Based on the Methods outlined in the EPC Methods Guide, we conducted additional pooled analyses for overall prescription rates for clinic-based education interventions, C-reactive protein (CRP) testing, and rapid strep testing used with a decision rule and for diarrhea and satisfaction for delayed prescribing.

One of the five systematic reviews included in this review had graded the strength of evidence (or the quality of the evidence using the GRADE system).[22,24-27] We assessed strength of evidence for key outcomes based on information provided in the reviews.

Table 2. Characteristics of included randomized controlled trials and observational studies

Study Characteristic	Category	All Studies	Educational	Communication	Clinical and POC	System Level	Multifaceted[a]
Design	RCTs (% Total, % Cluster RCT)	88 (69%, 27%)	37 (65%, 26%)	7 (100%, 86%)	33 (79%, 14%)	8 (62%, 38%)	13 (62%, 29%)
	Observational studies	40 (31%)	20 (35%)	0	9 (21%)	5 (38%)	8 (38%)
	Total (% of all studies)	*128 (100%)*	*57 (45%)*	*7 (5%)*	*42 (33%)*	*13 (10%)*	*21 (16%)*
Comparison	Versus usual care	*105 (82%)*	*55 (96%)*	*1 (14%)*	*27 (64%)*	*12 (92%)*	*12 (57%)*
	Head-to-head	*23 (18%)*	*2 (4%)*	*6 (86%)*	*15 (36%)*	*1 (8%)*	*9 (43%)*
	Total (% of all studies)	*128 (100%)*	*57 (45%)*	*7 (5%)*	*42 (33%)*	*13 (10%)*	*21 (16%)*
Study Quality	Good	18 (14%)	12 (21%)	0	6 (14%)	1 (8%)	2 (10%)
	Fair	96 (75%)	40 (70%)	5 (71%)	34 (81%)	9 (69%)	17 (80%)
	Poor	14 (11%)	5 (9%)	2 (29%)	2 (5%)	3 (23%)	2 (10%)
	Total (% of all studies)	*128 (100%)*	*57 (45%)*	*7 (5%)*	*42 (33%)*	*13 (10%)*	*21 (16%)*
Sample Size	Clinic/Clinician[f]	107,428	19,300	670	3,163	3,489	81,859
	Patient/Caregiver[g]	8,766,173	6,825,955	17,282	129,714	592,863	1,472,034
Population	Adult	35 (27%)	13 (23%)	3 (43%)	14 (33%)	3 (23%)	5 (24%)
	Child or both	93 (73%)	44 (77%)	4 (57%)	28 (67%)	10 (77%)	16 (76%)
	Total (% of all studies)	*128 (100%)*	*57 (45%)*	*7 (5%)*	*42 (33%)*	*13 (10%)*	*21(16%)*
Duration of Intervention	Range	3 w – 4.9 y	1 m – 4 y	3 m – 1 y	3 w – 3 y	6 m – 4 y	3 w – 4.9 y
Duration of followup	Range	1 d – 3 y	1 d – 17 m	28 d – 1 y	1 d – 2 y	2 w – 3 y	1 w – 2 y
Location	United States	57 (45%)	32 (56%)	1 (14%)	11 (26%)	9 (69%)	10 (48%)
	Other	71 (55%)	25 (44%)	6 (86%)	31 (74%)	4 (31%)	11 (52%)
	Total (% of all studies)	*128 (100%)*	*57 (45%)*	*7 (5%)*	*42 (33%)*	*13 (10%)*	*21 (16%)*
Multisite or Single Site[h]	Multisite	99 (79%)	42 (76%)	7 (100%)	28 (67%)	12 (92%)	20 (95%)
	Single Site	27 (21%)	13 (24%)	0	14 (33%)	1 (8%)	1 (5%)
	Total (% of all studies)	*126 (100%)*	*55 (44%)*	*7 (6%)*	*42 (33%)*	*13 (10%)*	*21 (17%)*
Type of Infection Targeted[i]	Acute bronchitis	29 (23%)	12 (21%)	1 (14%)	4 (10%)	5 (38%)	10 (48%)
	Acute Otitis media	39 (30%)	20 (35%)	1 (14%)	6 (14%)	6 (46%)	10 (48%)
	Sore throat/pharyngitis/tonsillitis	52 (41%)	20 (35%)	2 (29%)	14 (33%)	8 (62%)	12 (57%)
	Rhinitis	8 (6%)	4 (7%)	1 (14%)	1 (2%)	2 (15%)	2 (10%)
	Sinusitis	27 (21%)	8 (14%)	1 (14%)	5 (12%)	5 (38%)	10 (48%)
	Cough and common cold	25 (20%)	11 (19%)	4 (57%)	10 (24%)	1 (8%)	4 (19%)
	Any Acute RTI	79 (62%)	36 (63%)	5 (71%)	24 (57%)	8 (62%)	13 (62%)
	Total (% of all studies)	*128 (100%)*	*57 (45%)*	*7 (5%)*	*42 (33%)*	*13 (10%)*	*21 (16%)*

Table 2. Characteristics of included randomized controlled trials and observational studies (continued)

Study Characteristic	Category	All Studies	Educational	Communication	Clinical and POC	System Level	Multifaceted[a]
Key Question Addressed[i]	KQ 1 – Appropriate antibiotic prescription or use	106 (83%)	41 (72%)	7 (100%)	36 (86%)	13 (100%)	20 (95%)
	KQ 2 – Antibiotic resistance	2 (2%)	1 (2%)	0	1 (2%)	0	0
	KQ 3 – Medical complications[b]	18 (14%)	5 (9%)	2 (29%)	12 (29%)	1 (8%)	3 (14%)
	KQ 4 – Other clinical outcomes[c]	61 (48%)	29 (51%)	5 (71%)	22 (52%)	4 (31%)	10 (48%)
	KQ 5 – Intermediate outcomes[d]	15 (12%)	11 (19%)	2 (29%)	1 (2%)	0	0
	KQ 6 – Nonclinical adverse events[e]	6 (5%)	2 (4%)	1 (14%)	2 (5%)	2 (15%)	1 (5%)
	Total (% of all studies)	*128 (100%)*	*57 (45%)*	*7 (5%)*	*42 (33%)*	*13 (10%)*	*21 (16%)*

KQ = Key Question, m = month, POC = point of care, RTI = respiratory tract infection, RCT = randomized controlled trial, w = weeks, y = year(s)

Note: study counts include *only* primary studies (*not* companion studies or secondary publications); studies may be counted in more than one intervention category; column percentages reflect percent of studies in a single intervention category.

[a] Multifaceted is defined as more than one intervention category included in a single arm

[b] Medical complications (e.g. mortality, hospitalization, medical complications, adverse drug effects).

[c] Other clinical outcomes (e.g. clinic and/or ED visits, time to return to work and/or school, patient satisfaction, quality of life, improvement/speed of improvement of symptoms, use of nonantibiotic treatments).

[d] Intermediate outcomes (e.g. improved knowledge regarding use of antibiotics for acute RTIs, improved shared decisionmaking and improved clinician skills).

[e] Nonclinical adverse events (e.g. increased time burden on clinicians, patients, clinic staff).

[f] Reflects the sum of clinics and healthcare providers.

[g] Reflects the sum of patients (children and adults), parents of patients, families, patient records, patient visits, and infection episodes.

[h] Multisite or single site status could not be ascertained from 2 studies of educational interventions.

[i] Individual studies often targeted more than one infection type or pertained to more than one Key Question, resulting in sums that exceed total study counts.

Key Question 1. For patients with an acute respiratory tract infection, what is the comparative effectiveness of particular strategies in improving the appropriate prescription or use of antibiotics compared with other strategies or standard care?

Key Points

Educational Interventions

- Low-strength evidence based on two good-quality and one fair-quality observational studies suggested that public campaigns aimed at educating parents resulted in moderately reduced overall antibiotic prescribing, particularly for acute otitis media (AOM), but campaigns aimed at adults were not found effective. The effect in prescribing for children may be sustained over several months postintervention.
- Moderate-strength evidence based on two fair-quality trials and one good-quality observational study indicated that clinic-based educational interventions aimed at parents were effective when aimed at a broader age group (up to age 14) for any acute RTI, but low-strength evidence based on one good-quality trial showed no impact on prescribing for children ≤24 months with AOM
- Low-strength evidence based on four fair-quality observational studies suggested that educational interventions aimed only at clinicians resulted in small reductions in overall antibiotic prescribing for acute RTIs, prescribing for upper respiratory tract infection (URTI) and AOM, but no difference for acute sinusitis or pharyngitis.
- Moderate-strength evidence from five fair-quality trials and four fair-quality observational studies suggested that combining patient/parent and clinician education resulted in modest reductions in overall antibiotic prescribing and also in inappropriate prescribing for acute RTI compared with usual care.

Communication Interventions

- Moderate-strength evidence from five fair-quality trials indicated that interventions to improve communication between clinicians and patients results in moderate to large reduction in overall prescribing of antibiotics for acute RTIs compared with usual care.

Clinical Interventions

Delayed Prescribing

- Moderate-strength evidence based on three good-quality and three fair-quality trials suggested that delayed prescribing reduces overall prescription use compared with immediate prescribing.
- Low-strength evidence based on two fair-quality trials suggested no significant differences in overall antibiotic use between various strategies of delaying prescribing.

Clinical Scoring Tool

- Low-strength evidence based on one fair-quality trial suggested that the FeverPAIN clinical score modestly reduces overall antibiotic prescribing compared with leaving prescriptions for collection in (mostly adult) patients with sore throats.

Point-of-Care Tests

- CRP point-of-care testing
  - Moderate-strength evidence based on five fair-quality trials suggested that the use of CRP testing results in a moderate reduction in overall prescription and/or use of antibiotics for acute RTI compared with usual care.
- Procalcitonin point-of-care testing
  - Moderate-strength evidence based on one good-quality systematic review (of four trials) indicated that use of a procalcitonin algorithm results in a large reduction in overall antibiotic prescribing for adult patients with URTI or acute bronchitis presenting to primary care or emergency departments (EDs), and those presenting to primary care with URTI or lower respiratory tract infection (LRTI).
  - Low-strength evidence based on one good-quality trial suggested that in children ages 1 to 18 presenting to an ED with LRTIs, use of an adult procalcitonin algorithm resulted in a significantly *greater* overall prescribing of antibiotics.
- Point-of-care viral testing
  - Moderate-strength evidence based on four fair-quality trials suggested that point-of-care viral testing for influenza does not decrease overall antibiotic prescribing in children, while evidence in adults, based on one fair-quality trial, was insufficient.
  - Low-strength evidence, based on a fair-quality trial, that overall antibiotic prescribing was lower with a test for 13 respiratory viruses in adults with acute RTIs.
- Point-of-care streptococcal antigen testing (rapid strep testing)
  - There was low-strength evidence based on one fair-quality trial that use of point-of-care rapid strep testing results in lower overall antibiotic prescribing for pharyngitis compared with usual care with a wide range in reductions.

System-Level Interventions

- There was moderate-strength evidence from two fair-quality trials that electronic decision support systems improve overall antibiotic prescribing when the systems were used at least 50 percent of the time. Moderate-strength evidence based on two fair-quality trials that measures of appropriate prescribing were improved with electronic decision support systems in acute bronchitis and AOM compared with usual care.

Multifaceted Interventions

Multiple Interventions From Different Categories

- Based on two fair-quality trials, there was low-strength evidence that multifaceted interventions that combine clinician education and audit and feedback components do not statistically significantly reduce overall antibiotic prescribing for children with acute RTI.
- There was low-strength evidence from three fair-quality observational studies that a multifaceted intervention combining patient and clinician education plus audit and feedback was more effective than usual care in reducing overall antibiotic prescribing in adults with bronchitis (24% to 26% more), but not for other RTIs, and also not for various RTIs in the elderly or in children with acute pharyngitis.
- Based on one fair-quality trial and one fair-quality observational study, there was low-strength evidence that combined patient and clinician education plus communication training plus audit and feedback may reduce overall prescribing by 12 percent.

- There was low-strength evidence based on four fair-quality observational studies that, compared with usual care, combining provider and patient education with use of CRP testing leads to a large significant reduction in overall antibiotic prescription across various infection types and that this is largely due to the CRP testing component.
- There was low-strength evidence based on two fair-quality trials that rapid strep testing plus a decision rule can achieve lower rates of overall antibiotic prescribing for sore throat than usual care and delayed prescribing.

Augmentation (Adding a Second Type of Intervention Compared With One Component Alone)

- There was moderate-strength evidence based on two fair-quality trials that the combination of training in use of CRP and communication skills is superior to communication training alone but not superior to CRP training alone in reducing overall antibiotic prescribing in adults with acute RTI, particularly those with LRTIs.
- There was moderate-strength evidence based one two fair-quality trials that rapid step testing plus a decision rule results in lower rates of overall antibiotic prescribing for sore throat compared with the decision rule alone. Low-strength evidence based on one fair-quality trial found no difference in overall prescribing between the combination and rapid strep testing alone.
- Moderate-strength evidence based on a single large, fair-quality trial indicated that adding a clinical decision support system to a community education program on treating acute RTIs in children significantly improves *appropriate* antibiotic prescribing
- Low-strength evidence from a single fair-quality trial indicated that adding communication training to clinician education did not improve *appropriate* or overall prescribing.

Detailed Synthesis

Educational Interventions

Education Interventions Aimed at Patients or Parents

Seven studies of an educational intervention strategy for education of patients or parents, four trials and four observational reported the outcome of antibiotic prescribing.[41,76,105,124,135,144,149,163] These studies were mostly good quality. Five focused on educating parents about appropriate prescribing of antibiotics for acute RTIs in their children and two were directed at adult patients (see Appendixes D and F, and Table 3 below). Interventions varied across the study designs, with three evaluating community or national campaigns, and four examining clinic-based interventions. As these were very different approaches (one being more passive and the other being more active), they were considered separately. All of these reported *overall* prescribing of antibiotics.

Clinic-Based Interventions

Moderate-strength evidence from one good-quality RCT[85] and one fair-quality RCT[41,76] that evaluated simple clinic-based interventions aimed at reducing prescribing for any acute RTI in children (ages 6 months to 14 years) suggested a benefit of the interventions (pooled odds ratio 0.39; 95% CI 0.26 to 0.58). An observational study (pre-post design) with a similar intervention

and patient population found similar results, although not statistically significant, possibly due to lack of statistical power. (Table 3).[135]

A good-quality trial that aimed its intervention only at parents of younger children with AOM provides low-strength evidence to determine an impact on prescribing.[124] In this study (N=499), parents were given a take-home educational video featuring a clinic pediatrician when the child was healthy (with 2 followup interventions) and measured antibiotic prescribing for AOM or sinusitis over a 12-month period, finding no difference in prescribing compared with the control group (Table 3).[124]

Public Campaigns

Three observational studies of public campaigns reported highly variable results, depending in part on the intervention, the comparator, the population (adult or child), outcome measure and how it was ascertained.[144,149,163] Based on these studies we find low-strength evidence that public campaigns reduce antibiotic prescribing significantly in children with acute RTI (particularly for AOM and among those in managed care), but not in adults. Two of these studies, both using comprehensive public campaigns strategies, found reduced prescribing in children with acute RTIs.[144,149] A large study in Colorado found a significant reduction only in children seen in managed care (Table 3). The magnitude of effect appeared to range from 6 to 30 fewer prescriptions per 1000 persons per month (p=0.02). There were no details about specific infections, provider characteristics, or other potential sources of heterogeneity across the studies. Based on several time points before, during the 4-month intervention period and after the campaign, it is clear that the impact of the campaign reached its zenith at 4 months, regardless of which dataset were used (general public vs. managed care) and that there was regression to the mean after the intervention ended in the general and adult managed care groups, but not in the pediatric managed care group. An Israeli study aimed the intervention at parents of young children and found significant reductions in prescriptions for AOM, URTI, and pharyngitis. While all were statistically significant, the reduction for AOM was the largest and the reduction for pharyngitis was very small (see Table 3 below).[149]

A study from England found no impact of a national campaign using only posters advertised in magazines and newspapers, and in some clinics on prescribing of antibiotics for adults with acute RTI. The control group may have had some exposure to the campaign however, and there was guidance published by the National Institute for Clinical Excellence on advising using "delayed prescribing" techniques for acute self-limiting RTIs during the study period. Both of these may have reduced the ability to detect an impact of the campaign.[163] Similarly, the study using a comprehensive public campaigns campaign in Colorado that found an impact in children found no reduction in prescribing for adults with acute RTI treated in managed care, or in estimates of overall antibiotic prescribing in the general public (any reason, any antibiotic) (Table 3).[144]

Outcomes by Subgroups

Assessment of important factors that may contribute to heterogeneity was restricted by the limited reporting of these factors.

Diagnosis

A public campaign intervention in Israel found the greatest effect in reducing prescriptions in children for AOM (OR 0.65; 95% CI 0.59 to 0.72), with much smaller effects in URTI (OR 0.75; 95% CI 0.69 to 0.81) or pharyngitis (OR 0.92, 95% CI 0.89 to 0.97).[149] Other studies did not

separate results by diagnosis. As noted above, studies of public campaigns did not find any effect in adults, but did find reductions in prescribing for children.[144,163]

Education Level

In a study of a brief educational talk by the physician at the time of prescribing a delayed antibiotic approach, a lower level of mother's education was found to increase the decision to give antibiotics ($p<0.05$).[113]

Seasonal Effects

A trial of a locally tailored educational video for parents found no impact of the intervention overall, and also found no difference in the results based on winter versus summer time periods.[124]

Local Tailoring

All of the RCTs in this group of studies were locally created and tailored interventions, such that pooling of results was not possible. The two public campaigns interventions that were found effective in reducing prescribing in children involved elements that were locally tailored (e.g., culturally and language appropriate messages based on demographics),[144,149] while the more limited public campaigns intervention aimed at adults did not include such elements.[163]

Table 3. Patient education intervention studies

Intervention Type	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Clinic-Based Interventions	Taylor, 2003[124] N=499 <24 months AOM or sinusitis Good quality	RCT March 2000 – October 2001 12 mo. followup	Intervention: Take-home video featuring clinic pediatrician; pamphlet followup 6 weeks and 6 months after. Control: Injury prevention pamphlet.	Mean number of antibiotics prescribed per patient diagnosed: AOM: 1.7 vs. 1.9; p=0.23 AOM or sinusitis: 1.9 vs. 2.1; p=0.24
	Alder, 2005[41] N=40 1−10 y, acute RTI Fair quality	RCT August – December 2000	Intervention: Pamphlet and fact sheet. Control: nutrition education	Risk for antibiotic prescription (multiple logistic regression): OR 0.40 (95% CI 0.08 to 1.92)
	Francis, 2009[76] N=558 6 mo. – 14 y, acute RTI <7 days Good quality	cluster RCT October 2006 – April 2008	Intervention: Interactive book used during visit to foster discussion. Control: Injury prevention pamphlet.	Antibiotics prescribed: 22.2% vs. 42.2% (−20%) OR 0.39 (95% CI 0.26 to 0.59)
	Pshetizky, 2003[113] N=81 Children 3 mo. – 4 y AOM Good quality	RCT Winter of 1998 – 1999	Intervention: Watchful waiting + brief verbal education during visit. Control: Watchful waiting alone.	Effect of education on antibiotic use: 37% vs. 63% (−26%), p<0.0001 Proportion filling prescription: 40.9% vs. 86.5% (−45.6%) OR 0.11 (95% CI 0.03 to 0.36)
	Ashe, 2006[135] Patient N=720 6 mo.−10 y, acute RTI Good quality	Pre-Post November – December 2000 vs. 2001	Intervention: Waiting room posters. Control: Preperiod with no intervention.	Prescriptions per consultation: 41.9% vs. 48.6% (−6.7%) OR 0.76 (95% CI 0.56 to 1.04)

Table 3. Patient education intervention studies (continued)

Intervention Type	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Public Campaigns	McNulty, 2010[163] Patient N=1,888 pre and 1,830 post Adults Fair quality	Pre-Post January 2008 vs. 2009	Intervention: The English public antibiotics media campaign. (Advertisements in magazines and newspapers and posters made available to clinics and pharmacies. February 2008.) Control: Scotland (no campaign).	Reported Antibiotic Use (survey) Pre vs. Post Intervention Prescribed an antibiotic: England 34% vs. 35% (+1%), Scotland 29% vs. 35% (+6%) Scotland vs. England: (−5%); p=0.10
	Gonzales, 2008[144] Patient N=2,686,288 (in 2002) and 2,711,848 (in 2003) Children and adults Good quality	Prospective observational November 2002 – February 2003	Intervention: Mass media campaign in Denver, Colorado based on CDC's Get Smart program. (Billboards, various types bus ads, radio spots. Separate Spanish language interventions. Physician advocacy materials.) Control: Colorado Springs (no campaign).	Change in Antibiotic Prescribing: General population data: no difference, p=0.30 Study MCOs: Pediatric: reduced; p=0.01 Adult: No difference p=0.09
	Hemo, 2009[149] Patient N=Children with RTI diagnosis 101,401 pre, 84,979 post Good quality	Pre-Post Winter 2004 – 2005 vs. Winter 2005 – 2006	Intervention: A public campaigns campaign in Israel. (Radio and television ads; 4-part television series.) Control: Preintervention winter.	Antibiotic Purchase Rates, OR (95% CI): Children <18 years with acute RTI URTI: 0.749 (0.694 to 0.808) AOM: 0.652 (0.591 to 0.718) Pharyngitis: 0.931 (0.890 to 0.973)

CDC = Center for Disease Control, CI = confidence interval, MCO = Managed Care Organization, N = sample size, OR = odds ratio, p = p-value, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection

Educational Interventions for Clinicians

We identified three trials[84,128,131] and four observational studies[141,166,174,175] that evaluated the impact of educational programs for clinicians on appropriate prescribing of antibiotics for acute RTIs and reported on changes in antibiotic prescriptions (Table 4 and Appendix H). All but one study used some form of localized education materials and two specifically studied prescribing for children. Two of the trials were poor quality and not assessed here.[84,131] The remaining studies were fair quality, with one trial focusing only on sinusitis in adults,[128] two observational studies of acute RTIs in children,[141,166] and one of both adults and children.[175] The fair-quality trials were cluster randomized. The studies did not attempt to evaluate appropriateness of prescribing (vs. not prescribing).

These studies provided low-strength evidence that clinician-based educational interventions are effective in reducing overall antibiotic prescribing for acute RTI, but the magnitude was modest and varied (range 1.4% to 10%). The effect varied depending on how the outcome was defined, the comparison intervention/group, the specific infection, and the study design and quality. For example, no effect was seen with a program focused only on adults with sinusitis.[128] This was the only trial in this group of studies, comparing an organized, expert-led discussion of a new guideline with usual care (similar groups left to discuss the guideline at their discretion), with the guideline itself mailed to all general practitioners in the area and a national campaign on rational use of antibiotics at the time of the study. The results indicated that the intervention produced an incremental increase in effect (1.4% difference). Two observational studies that targeted clinicians with known higher antibiotic prescribing rates at baseline found the largest impact (7% and 10% reductions).[141,174] Both studies of antibiotic use in children found a benefit of the intervention,[141,166] while studies in adults were mixed.[128,174] A fair-quality observational study found reduced prescribing for uncomplicated URTIs and AOM, but not pharyngitis.[166]

A fair-quality observational study assessing an intervention applied broadly across Ontario, Canada found a small initial drop in prescribing of antibiotics typically used in acute RTI that was maintained over a 2-year period of time.[175] This evidence is insufficient to draw conclusions about the sustainability of the intervention.

Outcomes by Subgroups

In further examining potential sources of heterogeneity we found that while all the observational studies found at least some significant differences, the one fair-quality trial found no effect. While this may suggest confounding in the observational evidence, the trial was small and may have been underpowered.

Table 4. Change in antibiotic prescribing after clinician education interventions (good- and fair-quality studies)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
van Driel, 2007[128] N=75 Adults with acute sinusitis Fair quality	Cluster RCT November 2004 – March 2005	Intervention: Small group (quality circle) discussion of new local guideline. Control: Independently discuss guideline.	Intervention 56.9% vs. control 58.3% Adjusted OR 0.63 (95% CI 0.29 to 1.37)
Vinnard, 2013[174] Provider N=28 Patient N=382 Adults with acute bronchitis, cough, pharyngitis, URTI Fair quality	Pre-Post February – August 2000, 2001 vs. February – August 2002, 2003	Intervention: Academic detailing for known high prescribers. Patients with prior acute RTI visit received mailings.) Control: No intervention.	Before vs after (change): Academic detailing: 43% vs. 33% (−10%); Patient mailings: 18.9% vs. 14.2% (−4.7%); Control: 57.8% vs. 58.6% (+0.8%) Compared with control adjusted Ratio of ORs of change for before vs after: Academic detailing: 2.80 (95% CI 1.32 to 5.95) Patient mailings: 1.66 (95% CI 0.73 to 3.80)
Chowdhury, 2007[141] Practice N=16 Children <5 y; acute RTI Fair quality	Prospective observational study Dates unclear	Intervention: WHO acute RTI guidelines explained by a pediatrician one time; restricted to clinics with high baseline prescribing. Control: No intervention.	Intervention: 71% vs. 86% (−15%) Control: 89% vs. 81% (−8%) Difference between groups: −7% (p-values not reported; data not available to calculate)
Razon, 2005[166] N=24 Children; acute RTI Fair quality	Pre-Post November – February 1999 – 2000 vs. 2000 – 2001	Intervention: 1-day seminar based on CDC principles given by pediatric infectious disease expert.	Pre vs. Post URTI: 13.8% vs. 11.5% (−2.3%); p<0.05 AOM: 93% vs. 87.4% (−5.6%); p<0.05 Pharyngitis: 83.7% vs. 83.4% (−0.3%); NS
Weiss, 2011[175] N=All Quebec Prescriptions for specific antibiotics Fair quality	January – December 2003 – 2004 vs. February 2005 – December 2007	Intervention: 2-page guidelines on prescribing for acute RTIs, urinary tract infections and *C. difficile*; support letters from key stakeholders	All antibiotics: −4.1 per 1000 population (95% CI −6.6 to −1.6) in the first year after implementation Difference remained stable over following 2 years.

AOM = acute otitis media, CDC = Centers for Disease Control, CI = confidence interval; N = sample size, OR = odds ratio, p = p-value, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection

Combined Educational Interventions for Clinicians and Patients

We identified five fair-quality studies focused on acute RTI in children,[65,73,74,164,170] seven that focused on adults[61,64,106,148,156,158,105] and one fair-quality observational study that examined a public campaign that was not specific to adult or pediatric populations.[177] These studies evaluated the impact of combined educational programs targeted at both patients and clinicians on appropriate prescribing of antibiotics for acute RTIs, with six RCTs[61,64,65,73,74,106] (Table 5 and Appendix D) and five observational studies (Appendix F).[148,156,158,164,170] one poor-quality trial [71] and one poor-quality observational study were not considered further in the synthesis of the evidence (Appendixes E and G).[162]

The trials randomized or assigned clinician study groups by practitioner or clinic and the specific composition of clinician education varied somewhat across the studies, with most involving small group sessions led by a local expert, using national campaign materials or local or national guidelines on appropriate use of antibiotics in acute RTI (Table 5). Some were focused on specific infections (e.g., AOM), while others were comprehensive. Patient education

most commonly took the form of educational pamphlets and waiting room posters reinforcing the key messages, with a few providing additional forms of education (e.g., an interactive computer program in waiting area).

Overall Prescribing

The remainder of the studies (5 fair-quality trials and 5 fair-quality observational studies) provided moderate-strength evidence that combined clinician/patient educational interventions are effective in reducing overall antibiotic prescribing for acute RTI, with a modest magnitude of effect that varied depending on patient age, the specific infection targeted, statistical analysis, and the study design (e.g., comparison group). Across the RCTs, the mean reduction in overall antibiotic prescriptions was 7.3 percent (95% CI 4.0 to 10.6) when intervention was compared with no intervention. Statistical pooling was not possible due to variation in data reporting.

Appropriate Prescribing

Moderate-strength evidence indicates that combining clinician and patient or parent education improves appropriate prescribing of antibiotics for acute RTI. Two studies evaluated the appropriateness of prescribing for either sinusitis[148] or pharyngitis[65] using duration of symptoms as the only criterion (i.e., symptoms longer than 7 days for sinusitis and 9 days for pharyngitis). A fair-quality trial of children with pharyngitis symptoms for less than 10 days found a combined education program to result in significant but moderate magnitude reduction in inappropriate prescribing (−10.4%; OR 0.62; 95% CI 0.54 to 0.75).[65] An observational study found that the combination of an interactive computer patient education module and clinician education in an urgent care clinic resulted in a significant increase in the proportion of patients appropriately prescribed an antibiotic for acute sinusitis (+27%; 51% to 78%; p<0.001), with appropriateness defined as having symptoms for at least 7 days.[148]

A fair-quality trial in adults examined the effect of posters in waiting areas showing poster-sized "commitment letters" stating their clinicians' intention to improve appropriate antibiotic prescribing and including information on appropriate antibiotic use and nonantibiotic treatments posted for 12 weeks starting in February.[105] Appropriateness of prescribing was determined based on a prespecified list of ICD-9 codes. Codes deemed to not require antibiotic treatment included acute nasopharyngitis, acute laryngopharyngitis, acute bronchitis, acute URTI, nonstreptococcal pharyngitis, and influenza. The method for determining which codes were appropriate and which were not was not described. Absolute percent change in inappropriate prescribing over 1 year after intervention (12 weeks) was −9.8 percent in the poster group and +9.9 percent in the control group (adjusted absolute difference −19.7%; 95% CI −5.8 to −33.04). This study also analyzed the risk of shifting away from ICD-9 codes deemed inappropriate and for change in use of antibiotic-appropriate codes and found no statistically significant effect.

Outcomes by Subgroups

Age

The impact of combined clinician and parent education programs on prescribing of antibiotics for acute RTI in children was inconsistent across two fair-quality cluster RCTs conducted by the same group of researchers when considering age of the child. The first was conducted in 12 practices in Massachusetts and while decreases were seen in both groups, overall antibiotic prescribing was reduced with the intervention.[73] In younger children (3 to <36 months), including only those present in both pre and post years and controlling for differences in prescribing at baseline, the intervention led to a reduction of 16 percent (95% CI 8 to 23). For

older children, 36 to <72 months, the adjusted difference was 12 percent (2% to 21%). In the more recent study, 16 communities were cluster randomized to intervention or control.[74] This study also found significant decreases in overall prescribing of antibiotics from baseline year to the end of followup at year 5 after adjustment for baseline prescribing, secular trends, gender and insurance type. However, in this community-based study, in children 3 to <24 months there was no additional decrease seen in the intervention group (−0.5%, p=0.69). For children 24 to <48 months (4.2%, p<0.01) and 48 to <72 months (6.7%, p<0.001), small statistically significant decreases were seen. This study also found differences by type of insurance. Children covered by Medicaid had statistically significant reductions in prescribing across the 3 age groups (−4.5%, −5.5% and −9%, p≤ 0.01), while only the 48 to <72 months groups had a significant reduction in children with commercial insurance (−5.1%, p<0.01).

An observational study evaluating a community-wide campaign aimed at reducing antibiotic prescribing in children found a reduction of 11 percent (95% CI 8 to 14).[164] This study found the reduction greatest among children age 1 to 5 years, particularly among black children (18% reduction). A second observational study focused interventions on AOM, and found a 16 percent reduction (OR 0.25, 95% CI 0.11 to 0.53) after intervention.[170]

Studies in adults showed some variation in findings based on the target infection and the intervention-control comparison. In a trial targeting adults presenting to EDs with acute RTI, patient and clinician education (compared with no intervention) led to reduced prescribing for uncomplicated URTI with a difference of 9 percent between groups, but not for acute bronchitis (difference <1%).[106] In contrast, the observational study of a patient interactive computer education module and clinician education described above found a large statistically significant reduction from baseline in overall antibiotic prescribing for acute bronchitis (−34%, p<0.001).[148] Antibiotic prescriptions for nonspecific URTIs were also reduced (−13%, p<0.001) while prescribing for pharyngitis or sinusitis did not change after the intervention. Similarly, in two related observational studies, combination patient and clinician education did not significantly reduce prescribing for pharyngitis (OR 0.53, 95% CI 0.23 to 1.18) or rhinosinusitis (OR 0.65, 95% CI 0.21 to 1.06).[156,158]

Two studies examined a potential dose-response effect in increasing the number or type of educational interventions. In a study of adults with acute RTI, continuous (monthly) education sessions reduced prescriptions by a smaller amount (3.5%) over annual seasonal education sessions than seen in the studies with no intervention as the control (mean 8.2%).[61] Intermediate reductions in prescribing of antibiotics was seen with the addition of clinician education specifically about acute cough in the setting of a national campaign aimed at educating patients about appropriate antibiotic use, difference of 6.5 percent.[64]

A study from Australia that incorporated public messaging and local clinician education about appropriate use of antibiotics for acute RTI in any age group, over a 4-year period, found little impact beyond pre-existing background efforts.[177] While the study reported modest but significant decreases over the intervention period, it was not clear that there were important decreases related to the intervention. There was a preintervention decrease in prescriptions for antibiotics most commonly prescribed for acute RTIs of −3.5 per 1000 general practitioners per year and a postintervention decrease of −2.2 per 1,000 general practitioners per year. While both are statistically significant (p<0.0001) compared with baseline, the difference between the rates was not significant (p=0.1). Community surveys indicated that in 1999, 10.8 percent of the community respondents had taken an antibiotic the last time they had a cough, cold, or flu. This number progressively decreased over the intervention years to a low of 7.4 percent in 2004 (change 3.4%).

Table 5. Change in antibiotic prescribing after patient and clinician education interventions

Population	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Adults	Meeker, 2014[105] Patient N=954 Fair quality	RCT February – April 2012	Intervention: Waiting room posters of clinician letters of commitment to appropriate antibiotic use. Control: No intervention.	Inappropriate[a] Antibiotic Prescribing, % (95% CI): Intervention: 43.5% vs. 42.8% (−9.8%) Control: 33.7% vs. 52.7% (+9.9%) Adjusted difference in change poster vs. control: −19.7% (95% CI −5.8 to −33.04)
	Chazan, 2007[61] N=200 providers N=168,644 patients Adults; RTIs Fair quality	RCT October 2000 – April 2003	Intervention: Monthly sessions; diagnostic tools; therapeutic recommendations. Control: Seasonal intervention (2-hour meeting + reminders for providers, educational leaflets for patients).	Total Antibiotic Prescribing: Intervention vs. Baseline (daily dose/1000 patients/day): Seasonal Intervention group: 23.2 vs. 27.8 Continuous Intervention group: 22.9 vs. 28.7 (p for difference between groups <0.0001) Percent Decrease in Antibiotic Prescribing: Continuous vs. Seasonal intervention: 20.0% vs. 16.5% (p<0.0001)
	Coenen, 2004[64] N=85 providers N=1,503 patients Adults; acute cough Fair quality	Cluster RCT February – April 2000 and 2001	Intervention: National campaign + guideline on acute cough, academic detailing, and postal reminder. Control: National campaign.	Percent change in antibiotic prescribing: −15.6% vs. −9.1%; % difference −6.5% OR 0.56 (95% CI 0.36 to 0.87)
	Metlay, 2007[106] IMPACT Patient N=5,500 Provider N=16 Adults; acute RTI Fair quality	Cluster RCT November – February 2003 – 2004 vs. November – February 2004 – 2005	Intervention: *Clinicians*: Trained clinical leaders taught sessions and site-specific data. *Patients*: waiting/exam room posters and brochures and an interactive video kiosk in waiting rooms. Control: No intervention.	Antibiotic prescribed: Combined URTI or acute bronchitis: Intervention groups: 10% (95% CI −18 to −2) Control groups: 0.5% (95% CI −3 to +5) URTI:9.5% vs. −0.3% (no variance reported) Acute bronchitis:5.0% vs. −5.7% (no variance reported)
	Harris, 2003[148] N=42 providers N=1,518 patients Adults; acute RTI Fair quality	Prospective nonrandomized controlled trial October 2000 – April 2001	Intervention: (1) provider educational session based on CDC recommendations, (2) examination room posters, (3) Patient computer-based education. (Full intervention completed; limited intervention did not complete). Control: Baseline.	Antibiotic prescribed: Baseline vs. Limited Intervention vs. Full Intervention (%, p of Intervention vs. Baseline, p for limited vs. full): Bronchitis: 58 vs. 30 vs. 24, p<0.001, NS Nonspecific URTI: 14 vs. 3 vs. 1, p<0.001, NS Pharyngitis: 76 vs. 71 vs. 78, p=NS, NS Sinusitis ≥ 7 days[a]: 51% vs. 83% vs. 78%; p<0.001 All ARI[a]: 45 vs. 31 vs. 35, p<0.001, <0.001

Table 5. Change in antibiotic prescribing after patient and clinician education interventions (continued)

Population	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Adults	Llor, 2011[156] N=339 providers N=6,849 Adults; pharyngitis Fair quality	Pre/post study with post-intervention control group. First registry January/ February 2008, second registry January/ February 2009.	Intervention: prescriber training and clinical guidelines; patient handouts. Control: 2 other communities with no intervention. (2nd intervention group also received point-of-care testing, evaluated elsewhere in report)	Adjusted odds ratio; 95% CI for antibiotic prescriptions in intervention vs. control: OR 0.53; 95% CI, 0.23 to 1.2
	Llor, 2012[158] N=338 providers N=5,385 patients Adults; LRTI Fair quality	Pre/post study with post-intervention control group. First registry winter of 2008, second registry winter of 2009.	Intervention: prescriber training and clinical guidelines; patient handouts. Control: 2 other communities with no intervention. (2nd intervention group also received point-of-care testing, evaluated elsewhere in report)	Adjusted odds ratio; 95% CI for antibiotic prescriptions of antibiotics in intervention versus vs. control groups: OR 0.42; 95% CI, 0.22 to 0.82
Children	Cohen, 2000[b65] Patient N=1,016 Parent N=NR Children ≤ 10 y; pharyngitis ≤ 9 days Fair quality	RCT Dates NR	Intervention: Educational material for parents and clinicians. Control: No intervention[c].	Change in number of inappropriate antibiotic prescriptions: 26.7% vs. 37.1% (−10.4%) OR 0.62 (95% CI 0.54 to 0.75)
	Finkelstein, 2001[b73] Patient N=8,815 Provider N=157 Children 3 to <72 mo. in 12 practices Fair quality	RCT December 1997 – November 1998	Intervention: *Clinicians*: Academic detailing by local trained peer leaders with CDC materials; 4-month reminder. *Parents*: CDC pamphlet; letter from pediatrician; waiting room posters/pamphlets. Control: No intervention.	Difference in antibiotics prescribed per-person year (per child, adjusted): 3 to <36 months: −7.1% (p<0.001) Analysis limited to patients in both baseline and followup data set: −16% (95% CI 8 to 23) 36 to <72 months: −5.2% (p<0.001) Analysis limited to patients in both baseline and followup data set: 12% (95% CI 2 to 21)

Table 5. Change in antibiotic prescribing after patient and clinician education interventions (continued)

Population	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Children	Finkelstein, 2008[74] Patient N=233,135 person-years Provider N=NR Children 3 to <72 months Fair quality	Cluster RCT October – March from 2000 – 2003	Intervention: *Clinicians*: Guideline dissemination, small-group education, prescribing audit/feedback, various items (e.g., prescription pads) with REACH Mass logo. *Patients* (parents): Brochure on appropriate antibiotic use, newsletters, interactive Web site, posters, etc. Control: No intervention.	Adjusted % change (over 3 years) 3 to <24 months: −20.7 vs. −21.2 (−0.5%; p=0.69) 24 to <48 months: −10.3 vs. −14.5 (−4.2%; p<0.01) 48 to <72 months: −2.5 vs. −9.3 (−6.7%; p<0.0001)
	Perz, 2002[164] Provider N=250 Patient N=464,200 person-years Children; ARTI Fair quality	Time series 12-month periods before (May 1996 through April 1997), during (1997/98) and after (1998/99) intervention.	Intervention: Lectures for providers; prescribing guidelines; newsletters, pamphlets; patient education materials; media coverage and public service announcements. Control: 3 urban counties with no intervention.	Change in antibiotic prescription rates (% reduction; 95% CI): −11%; 95% CI, −14 to −8 Ratio of antibiotic prescriptions to respiratory illness visits: White: −8% (−16 to 0) Black: −13% (−19 to 8)
	Smabrekke, 2002[170] Practice N=2 Patient N=819 Children aged 1−15 y; AOM Fair quality	Controlled before/after. December 1997 to March 1998 (baseline); December 1998 to March 1999 (intervention)	Intervention: Symposium for providers. Pamphlets and oral education for parents. Control: Similar community with no intervention	Percent prescribed antibiotic (before vs after) Intervention: 90% (318/355) vs. 74% (155/209), p<0.01 Control: 95% (126/133) vs. 91% (114/125), p=0.5
Mixed Population	Wutzke, 2007[177] Provider N=5,758 Patient N=12,217 Ages ≥ 15 y; URTI Fair quality	Before/after 1999 baseline, 2000 - 2004 intervention.	Intervention: Radio, television, and newspaper campaign. Implemented seasonally with community-based education sessions. Control: Precampaign.	Proportion of the community reporting taking antibiotics when ill with last cough, cold, or flu (% change, p) 1999 vs. 2000: 10.8 vs. 10.0 (- 0.8, NS) 1999 vs. 2001: 10.1 (- 0.7, NS) 1999 vs. 2003: 9.8 (- 1.0, NS) 1999 vs. 2004: 7.4 (−3.4, p<0.05)

AOM = acute otitis media, ARI = acute respiratory infection, CDC = Centers for Disease Control, CI = confidence interval, ECS = Emergency Call Service, GP = general practitioner, LRTI = lower respiratory tract infection, N = sample size, NS = not significant, OR = odds ratio, p = p-value, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection

[a] Codes deemed to not require antibiotic treatment included acute nasopharyngitis, acute laryngopharyngitis, acute bronchitis, acute URTI, nonstreptococcal pharyngitis, and influenza.

[b] Included in published systematic review[21]

[c] Abstract in English, primary study in French – included in published systematic review[21]

Communication Strategies

Strategies To Improve Clinician-Patient Communication Compared With Usual Care

We identified five fair-quality RCTs that compared interventions to improve clinician-patient communication with usual care and met inclusion criteria.[41,42,56,86,87,95] (two additional studies were poor quality[42,107]). These trials studied different interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs and reported on changes in antibiotic prescriptions (Table 6 and Appendix D). In fair-quality trials, the interventions targeted clinicians only in four trials[56,86,87,95] and patients only in one trial.[41] Two trials studied interventions specifically designed to improve shared decisionmaking, an approach in which the values, preferences, and opinions of both the patient and the clinician are made explicit and considered in the decision.[86,87] The second of these shared decisionmaking trials[86] studied a revised version of the intervention used in the first trial.[87] Two trials[56,95] were factorial designs aimed at clinicians that assessed two interventions – one to enhance communication skills and one to train clinicians in the use of point-of-care CRP testing, and another trial was a factorial design study aimed at patients only.[41] All of the clinician-based studies were cluster randomized, while the patient-based trial was not. All but one of the five clinician interventions involved some form of in person training by study personnel; one clinician intervention was mostly internet-based[95] and two others included some video or internet-based training.[86,87]

Five fair-quality studies evaluated the indirect outcome of *overall* prescription of antibiotics for acute RTIs.[41,56,86,87,95] These five studies consistently found communication interventions to reduce the relative risk of antibiotic prescription for acute RTIs compared with usual care (range from 0.17 to 0.69; Table 6), with findings statistically significant in all but one study.[87] Absolute risk reductions ranged from 9.2 to 26.1 percent. The heterogeneity of the various strategies and approaches to improving clinician-patient communication precluded a pooled analysis.

Outcomes by Subgroups

Although few studies conducted subgroup analyses, the general finding of an overall reduction in antibiotic prescribing was seen across studies that varied in the types of RTI included, signs and symptoms reported, age of patients (adult and child), and geographic region. All but one study was conducted during the winter and spring months, with no comparisons of effectiveness by time of year. A large study (clinician N=372; patient N=4264) reported on differences in overall prescribing according to LRTI versus URTI.[95] This study – which was predominantly aimed at patients with LRTIs (80%), but included patients with URTI (20%) – found the communication intervention to be associated with slightly lower relative risk of antibiotic prescribing for LRTIs (RR 0.67; 95% CI 0.46 to 0.88) than for URTIs (RR 0.78; 95% CI 0.43 to 1.21), but with overlapping confidence intervals. No other studies reported any subgroup analyses of possible differences in effectiveness according to factors such as patient characteristics, clinician characteristics, target of the interventions, diagnostic methods used, or other contextual factors.

While reductions were seen in all five studies, the reduction was greatest in the one study with an intervention aimed at patients only; a small fair-quality, factorial design trial that found a reduction in antibiotic prescribing of OR 0.17 (95% CI 0.03 to 0.93) compared with a usual care control group.[41]

Strategies To Improve Clinician-Patient Communication Compared With Point-of-Care C-Reactive Protein Testing (Head-to-Head Comparisons)

Two fair-quality trials compared strategies to improve clinician-patient communication with point-of-care CRP testing (Table 6, Evidence Table 1).[56,95] Both trials evaluated overall antibiotic prescribing, not appropriate prescribing specifically. Each used a different communication training intervention targeting clinicians. One trial (N=258), based on motivational interviewing, used in person training and simulated patients[56] and found no difference between communication training and CRP testing in reducing overall antibiotic prescribing for acute RTIs (RR 0.85; 95% CI 0.58 to 1.25). The other trial (N=4264) used a Web-based training program with illustrative video clips[95] and found communication training to be associated with a modestly higher relative risk of overall antibiotic prescription compared with CRP testing (RR 1.17; 95% CI 1.05 to 1.31).

Outcomes by Subgroups

Diagnosis

One of the trials reported on differences in overall prescribing according to URTI versus LRTI.[95] This study found no difference in the degree of reduction of antibiotic prescribing for communication training compared with CRP testing in patients with URTIs (28.3% vs. 27.4%; unadjusted RR 1.04; 95% CI 0.76 to 1.41) and modestly smaller reduction in patients with LRTIs (43.5% vs. 36.4%; unadjusted RR 1.20; 95% CI 1.07 to 1.34), but with overlapping confidence intervals. Neither study reported any subgroup analyses of possible differences in effectiveness according to factors such as patient characteristics, clinician characteristics, target of the interventions, diagnostic methods used, or other contextual factors.

Age

The magnitude of effect was larger in the single study of antibiotic prescribing in children compared with the studies in adults.

Table 6. Interventions to improve communication between clinicians and patients

Population	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Children	Alder, 2005[41] Practice N=2 Provider N=NR Patient N=80 Parents of child patients (1 to 10 y); acute ear pain, sore throat, cough, congestion and/or fever Fair quality	2 X 2 factorial RCT (patient level). August 2000 – December 2000 Followup: None	Intervention: *Communication*: Given four questions to ask clinician; role-playing exercises; breathing technique. *Education*: Information-only on antibiotic use. *Combination*: Communication + Education. Control: Information on general child nutrition.	Antibiotics prescribed at index visit: Communication vs. Control: OR (95% CI): 0.17 (0.03 to 0.93)
Adults	Cals, 2009[56] Practice N=20 Provider N=40 Patient N=431 Adults; suspected LRTI, cough <4 weeks Fair quality	2 X 2 factorial cluster RCT (clinic level). September 2005 – March 2006 and September 2006 – March 2007. Followup: 28 days for most patients (maximum 10 weeks).	Intervention: *Communication skills training*: based on 11 key tasks (e.g., exploring patient's fears and expectations, asking patient's opinion of antibiotics), and elicit-provide-elicit framework. Control: Usual Care	Antibiotics prescribed at index visit: Communication vs. Control: 33.3% vs. 66.7%; unadjusted RR 0.50 (95% CI 0.36 to 0.69) Communication vs. CRP: 33.3% vs. 39.1%; unadjusted RR 0.85 (95% CI 0.58 to 1.25)
	Little, 2013[95] Practice N=228 Provider N=372 Patient N=4,264 Patients (>18 y); acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster RCT (clinic level). February 2011 – May 2011. Followup: 4 weeks	Intervention: *Communication skills training*: Internet-based training in communication skills; interactive booklet; video demonstrations. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual care.	Antibiotic prescribing at index consultation (reported by clinicians): Communication + Combination vs. CRP + Control: 36% vs. 45%; adjusted[a] RR 0.69 (95% CI 0.54 to 0.87) Communication vs. Control: 41% vs. 58%; unadjusted RR 0.68 (95% CI 0.50 to 0.89) Communication vs. CRP: 41% vs. 35%; unadjusted RR 1.17 (95% CI 1.05 to 1.31) Communication vs. Control: URTI: adjusted[a] RR 0.82 (95% CI 0.53 to 1.18) LRTI: adjusted[a] RR 0.66 (95% CI 0.51 to 0.84)

Table 6. Interventions to improve communication between clinicians and patients (continued)

Population	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Mixed (adults and children)	Légaré, 2010[87] Practice N=4 Provider N=33 Patient N=459 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2007 – March 2008 Followup: 2 weeks	Intervention: Interactive workshops on URTIs, risk communication, fostering patient participation in decisionmaking, shared decisionmaking support tools. Control: Delayed intervention.	Used antibiotics immediately after consultation: Baseline: 56% vs. 54% After experimental group received intervention (Time 1): 33% vs. 49% After control group received intervention (Time 2): 35% vs. 46% Difference at Time 1 (95% CI): −16 (−31 to 1), p=0.08. Proportion who filled prescription: Baseline: 79% vs. 70% Time 1: 45% vs. 51% Difference at Time 1 (95% CI): −6 (−17 to 6), p=0.35.
	Légaré, 2012[86] Practice N=9 Provider N=149 Patient N=359 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2010 – April 2011 Followup: 2 weeks	Intervention: 2-hour online tutorial and 2-hour onsite interactive workshop on decisionmaking about antibiotic treatment for RTIs and communication with patients. Control: Usual care.	Antibiotic prescribing immediately after consultation: Baseline: 41.2% vs. 39.2% After intervention: 27.2% vs. 52.2% Absolute difference: 25.0% Adjusted RR (95% CI): 0.5 (0.3−0.7)

CI = confidence interval, CRP = C-reactive protein, LRTI = lower respiratory tract infection, N = sample size, OR = odds ratio, RCT = randomized controlled trial, RR = relative risk, RTI = respiratory tract infection, URTI = upper respiratory tract infection

[a]Adjusted for multiple factors, including clustering by physician and practice.

Clinical Interventions

Delayed Prescribing Strategies

We primarily relied on findings from a good-quality Cochrane review for evaluating the comparison of delayed prescribing strategies to immediate or no prescribing.[22] The Cochrane review included seven RCTs that reported antibiotic use outcomes.[44,60,70,90,94,96,122] The trials addressed comparisons of delayed versus immediate antibiotic prescriptions[44,70,90,94,96,122] and delayed versus no antibiotic prescriptions.[60,94,96] We included two additional trials that compared different methods of delaying prescriptions, including giving prescriptions with instructions, leaving prescriptions for collection, postdating prescriptions, or requesting recontact[92,133] and one trial that compared delayed prescribing to use of a clinical prediction score.[91]

Delayed Versus Immediate

There was moderate-strength evidence that delayed antibiotics result in significantly reduced antibiotic use compared with immediate antibiotics based on findings from six RCTs summarized in the 2013 Cochrane review by Spurling and colleagues.[22] The Cochrane review did not present results of their pooled analyses because of significant heterogeneity, which may have been due to the clinical diversity of participants that included adults and children with common cold, cough and sore throat, and AOM, type of delayed prescribing approach, (i.e., level of barrier to patient) and method of measuring use. We could not evaluate the potential effects of variability in any one of these factors because of the variability across the studies in the other factors. Compared with immediate prescribing, odds of reduced antibiotic use were greatest when the barrier to obtaining the delayed prescription was highest, requiring a return visit to reception (range of absolute differences: −63% to −76%; range of OR's [95% CI]: 0.00 [0.00-0.02] to 0.05 [0.02-0.08])[70,90,94,96] compared with when the delayed prescription was issued to the patients with instructions to delay (range of absolute differences: −34% to −49% OR 0.09; 95% CI 0.05 to 0.17 to 38% vs. 87%; OR 0.20; 95% CI 0.09 to 0.44).[44,122] All studies used indirect methods for measuring antibiotic use, ranging from documentation of filling the prescription to patient diary documentation of daily consumption. Because of the variability reliability of these indirect methods in measuring actual use, caution should be taken in interpreting these findings.

Antibiotic use rates ranged from 33 to 44 percent for different methods of delaying prescriptions.[92,133]

Delayed Versus Delayed

Compared with issuing a prescription with instructions to delay, there was low-strength evidence that alternative delaying strategies do not lead to further reductions in antibiotic use, including postdating the prescriptions (OR 1.05; 95% CI 0.68 to 1.62), leaving prescriptions for collection (OR 1.32; 95% CI 0.68 to 2.58), or requesting recontact (OR 1.11; 95% CI 0.58 to 2.11).

Delayed Versus Clinical Prediction Score

There was low-strength evidence from the fair-quality PRISM RCT (primary care streptococcal management) that use of the FeverPAIN clinical score (features: fever during previous 24 hours; purulence; attends rapidly (within 3 days after onset of symptoms); inflamed tonsils; no cough/coryza; immediate antibiotics for score ≥4, delayed antibiotics for scores of 2−3, and no antibiotics for scores of 0−1) statistically significantly reduced overall antibiotic use

compared with using a delayed prescription strategy of leaving the prescription for collection after 3−5 days (37% vs. 46%; RR 0.71; 95% CI 0.50 to 0.95).[91]

Outcomes by Subgroups

Although there was variation across studies in antibiotic use, it was difficult to determine whether it is due to any particular subgroup characteristic of interest as studies differed on multiple factors, including type of RTI, type of delay strategy, type of clinic, geographic region, and time period. For example, the study with the greatest reduction in overall antibiotic use (OR 0.00; 95% CI 0.00 to 0.07) involved patients with cough who were seen in general practitioners offices in Scotland between December 1997 and November 1998 who were required to wait a week before returning for their delayed prescription.[70] In contrast, the study with the smallest reduction in overall antibiotic use (OR 0.20; 95% CI 0.09 to 0.44) involved patients with the common cold who were seen in family practice clinics during an unspecified time period who were given the delayed prescription at the time of the visit and only instructed to wait 72 hours.[44]

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

C-Reactive Protein Testing Compared With Usual Care

We primarily relied on findings from a good-quality Cochrane review for evaluating C-reactive protein (CRP) testing for acute RTI compared with usual care.[27] The Cochrane review included six RCTs that reported on antibiotic prescribing outcomes (Table 7).[56,58,68,95,179,180] All six studies had a low to moderate risk of bias and were conducted in primary care settings. Five of the six studies were conducted in Europe and one trial[179] was conducted in Russia. The studies varied in the type and amount of guidance provided to clinicians for interpreting CRP test results and making antibiotic prescription decisions. None of the studies reported using either cardiac CRP (c-CRP) or high sensitivity CRP (hsCRP) assays and are presumed to have used general CRP assays. Five trials used guidelines with two to four defined levels of CRP and suggested or stated that either 50 mg/L[179,180] or 100 mg/L[56,58,95] is a threshold at which antibiotics would likely be indicated. One trial provided no explicit guidance, but indicated that CRP <10 mg/L is normal and that CRP <50 mg/L is seldom due to bacterial infection.[68] Two of the studies were clinic cluster-randomized 2 x 2 factorial trials of CRP testing and an intervention to improve communication between clinicians and patients.[56,95] A third study was a simple clinic cluster-randomized trial of CRP testing compared with usual care.[179] The remaining three trials were each randomized at the level of the patients.[58,68,180] We also found another systematic review that included a broader range of studies (13). This review was rated poor quality primarily due to an error in the meta-analysis.[25]

We included two additional fair-quality studies that compared CRP testing with usual care – one RCT that used CRP testing only in conjunction with white blood cell (WBC) measurement,[123] and one observational study.[137] The RCT was conducted in a hospital-affiliated outpatient clinic in Japan[123] and the observational study was conducted among general practitioners in Denmark.[137] The RCT was excluded from the Cochrane review on the basis of not being in a primary care setting;[27] however, hospital-affiliated outpatient clinics were included in our protocol. The observational study was excluded from the Cochrane review based on study design, but included in our protocol. The RCT did not describe any clinical guidance and indicated that physicians used a "reference level" of CRP ≤5 mg/L.[123] In the observational study,

CRP levels were reported to clinicians in five categories ranging from 0-9 mg/L to >100 mg/L, but no explicit prescribing guidance was provided.[137]

The Cochrane review concluded that there was moderate-quality evidence (GRADE) that CRP testing for acute RTIs was associated with lower antibiotic prescribing compared with usual care.[27] In pooled analyses of six trials (N=3284),[56,58,68,95,179,180] the relative risk for prescribing at the index consultation was lower in the CRP group (RR 0.78; 95% CI 0.66 to 0.92; I^2=68%); and in pooled analyses of four trials (N=708),[56,58,179,180] the relative risk for prescribing within 28 days of the index consultation was also lower in the CRP group (RR 0.80; 95% CI 0.67 to 0.96; I^2=40%). In stratified analysis, the relative risk of antibiotic prescribing at the index consultation was lower for cluster-RCTs (three trials; RR 0.68; 95% CI 0.61 to 0.75; I^2=0.0%) compared with those that randomized at the patient level (three trials; RR 0.90; 95% CI 0.80 to 1.02; I^2=5%) with no significant heterogeneity in either group. The relative risk of antibiotic prescribing within 28 days was slightly lower for cluster-RCTs (two trials; RR 0.68; 95% CI 0.51 to 0.91; I^2=19%) compared with those that randomized at the patient level (two trials; RR 0.87; 95% CI 0.75 to 1.02; I^2=7%) with no significant heterogeneity in either group but with overlapping confidence intervals.

Two of the six studies in these pooled analyses were cluster-randomized 2 x 2 factorial trials of CRP testing in addition to an intervention to improve communication between clinicians and patients around antibiotic prescription for RTIs. In their pooled analyses, the Cochrane review compared all patients who received CRP testing with all patients who did not receive CRP testing. Both groups included some patients whose physicians had received the communication intervention, which might mute an observed effect of CRP testing. To better characterize the specific effect of CRP testing alone compared with usual care (i.e., no intervention) – which is the question of interest for the current review – we conducted a pooled analysis of the same six studies (N=3,650) included in the Cochrane review, but using the data for the groups that received CRP testing only compared with the groups that received usual care.[56,58,68,95,179,180] The relative risk for prescribing at the index consultation was lower in the CRP group (RR 0.73; 95% CI 0.60 to 0.90; I^2=85%) (Figure 3); a greater difference than in the Cochrane review (RR 0.78).

The two additional studies that we included also found CRP testing to be associated with lower prescribing of antibiotics for acute RTIs compared with usual care. One trial (N=301) found that patients receiving CRP testing in conjunction with WBC testing were less likely to receive antibiotics [57.5% vs. 91.0%; unadjusted RR 0.63 (95% CI 0.52 to 0.74)].[123] The single observational study found that general practitioners with access to CRP tests prescribed antibiotics for acute sinusitis less frequently than those without access to CRP tests (59% vs. 78%; OR 0.43; 95% CI 0.33 to 0.58).[137]

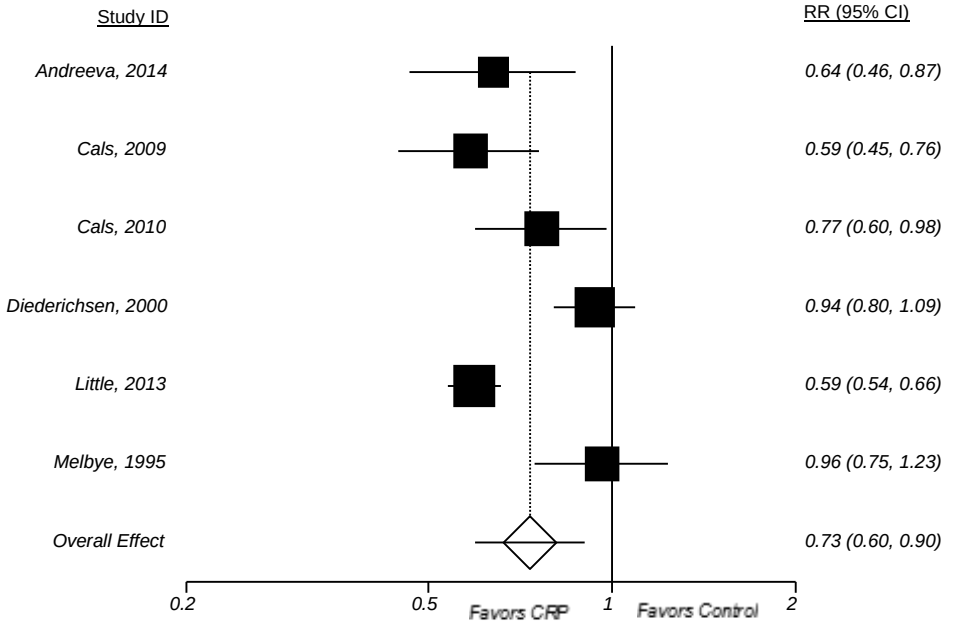
Outcomes by Subgroups

Although few studies conducted subgroup analyses, the general finding of an overall reduction in antibiotic prescribing was seen across studies that varied in the types of RTI included, signs and symptoms reported, age of patients (adult and child), and country. Seven of the eight studies were conducted during the winter months and some also included spring and autumn months, with no comparisons of effectiveness by time of year. The eighth study was published in Norwegian – precluding our extracting any information beyond that reported in the Cochrane review, which did not report on the time of year the study was conducted.[180]

Diagnosis. Three studies reported on differences in prescribing according to the anatomical site of the RTI. A large trial (practice N=123; patient N=1,932) found no difference in the

effectiveness of CRP testing (compared with usual care) when used in patients with upper respiratory infections (URTIs) compared to those with lower respiratory infections (LRTIs). For patients with URTIs, the adjusted relative risk (95% CI) of antibiotic prescribing was 0.48 (0.23 to 0.87), and for those with LRTIs it was 0.53 (0.35 to 0.74), with overlapping confidence intervals.[95] Another trial (clinician N=33; patient N=258) found no difference in the effectiveness of CRP testing in rhinosinusitis compared with LRTIs, with unadjusted relative risks of 0.75 vs. 0.81, respectively, and overlapping 95% confidence intervals of (0.55 to 1.02) and (0.53 to 1.03).[58] A third trial reported no difference in antibiotic prescribing between the CRP testing group and the usual care group according to anatomic location of RTI (middle ear, sinus, chest, other), with results presented diagrammatically as overlapping confidence intervals but with no statistical test results.[68]

Figure 3. Overall antibiotic prescribing with C-reactive protein testing compared with usual care



CI = confidence interval, CRP = C-reactive protein, RR = relative risk

CRP Testing Compared With Other Strategies (Head-to-Head Comparisons)

Two fair-quality trials compared CRP testing with strategies to improve communication regarding the prescribing of antibiotics for acute RTIs between clinicians and patients, coming to different conclusions (Appendix D).[56,95] These studies are described in detail in the section on strategies to improve communication between clinicians and patients (above). Each of the trials used a different communication training intervention targeting clinicians, one finding no difference between CRP testing and communication training in reducing overall antibiotic prescribing for acute RTIs (RR 1.17; 95% CI 0.80 to 1.72)[56] and the other finding the use of CRP testing to modestly reduce the overall antibiotic prescribing for acute RTIs (RR 0.85; 95% CI 0.77 to 0.95).[95] This evidence is insufficient to draw conclusions.

One fair-quality study compared the effectiveness of a clinical algorithm with and without point-of-care CRP testing as part of the algorithm in an urban emergency department.[80] This

study was excluded from the Cochrane review on the basis of not being in a primary care setting;[27] however, emergency departments were included in our protocol. The algorithm was used to guide chest x-ray and antibiotic treatment decisions for acute cough illness. Low-strength evidence from this study suggested no statistically significant difference in antibiotic prescribing when CRP testing was included as part of the algorithm compared with use of the clinical algorithm alone (37% vs. 31%; RR 1.23; 95% CI 0.77 to 2.00). This evidence is insufficient to draw conclusions (Appendix J).

Outcomes by Subgroups

Diagnosis. The larger trial (N=420) reported no difference in the degree of reduction of antibiotic prescribing with CRP testing compared with communication training in patients with URTIs (27.4% vs. 28.3%; unadjusted RR 0.97; 95% CI 0.71 to 1.32) and a modestly greater reduction in patients with LRTIs (36.4% vs. 43.5%).[95]

Table 7. C-reactive protein point-of-care testing interventions

Study and Characteristics		Study Details	Intervention and Control Details	Outcomes
RCTs	Andreeva, 2013[179] Practice N=18 Provider N=18 Patient N=179 Adults ≥18 y; first consultation for acute cough or LRTI; illness <28 days Fair quality	Cluster RCT (provider level) January 2010 – April 2010 Followup: 2 weeks	Intervention: CRP testing during consultation, with guidance on interpretation. Control: usual care (clinical assessment only). Both groups received training in acute cough/LRTI and CRP testing.	Antibiotic treatment at index visit: 37.6% vs. 58.9%; unadjusted RR 0.64 (95% CI 0.47 to 0.87). Antibiotic within 2 weeks of index visit: 40.6% vs. 71.8%; unadjusted RR 0.57 (95% CI 0.43 to 0.74).
	Cals, 2009[56] Practice N=20 Provider N=40 Patient N=431 Adults; suspected LRTI, cough <4 weeks Fair quality	2 X 2 factorial cluster trial. September 2005 - March 2006 and September 2006 - March 2007. Followup: 28 days for most patients (maximum 10 weeks).	Intervention: *CRP testing*: testing during consultation, with guidance on interpretation. *Communication skills training*: based on 11 key tasks (e.g., exploring patient's fears and expectations, asking patient's opinion of antibiotics), and elicit-provide-elicit framework. *Combination*: CRP + Communication. Control: usual care.	Antibiotics prescribed at index visit: CRP + Combination vs. Communication + Control: 30.8% vs. 52.9%, p=0.02 (adjusted model); CRP vs. Control: 39.1% vs. 66.7%; CRP vs. Communication: 39.1% vs. 33.3%; Antibiotic within 28 days of index visit: CRP + Combination vs. Communication + Control: 44.9% vs. 58.3%, p<0.01 (adjusted model)
	Little, 2013[95] Practice N=228 Provider N=372 Patient N=4,264 Patients (>18 y); acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster trial. February 2011 – May 2011. Followup: 4 weeks.	Intervention: *CRP testing*: testing during consultation, with guidance on interpretation and prescribing. *Communication skills training*: internet-based training in communication skills; interactive booklet consultations; video demonstrations. *Combination*: CRP + Communication. Control: usual care.	Antibiotic prescribing at index consultation (reported by clinicians): CRP + Combination vs. Communication + Control: 33% vs. 48%; adjusted[c] RR 0.54 (95% CI 0.42 to 0.69) CRP vs. Control: 35% vs. 58%; unadjusted RR 0.59 (95% CI 0.54 to 0.66) CRP vs. Communication: 35% vs. 41%; unadjusted RR 0.85 (95% CI 0.77 to 0.95) URTI: adjusted[c] RR 0.50 (95% CI 0.31 to 0.79) LRTI: adjusted[c] RR 0.53 (95% CI 0.39 to 0.68)

Table 7. C-reactive protein point-of-care testing interventions (continued)

Study and Characteristics		Study Details	Intervention and Control Details	Outcomes
RCTs	Cals, 2010[58] Practice N=11 Provider N=33 Patient N=258 Adults (≥ 18 y); first consultation for LRTI or rhinosinusitis Fair quality	November 2007- April 2008. Followup: 28 days.	Intervention: CRP testing during consultation. Clinicians advised to combine CRP results with clinical findings. Control: usual care (immediate, delayed, or no antibiotics).	Antibiotic prescribing after index visit (used immediately or filled a delayed prescription): Overall: 43.4% vs. 56.6%; adjusted[a] RR 0.77 (95% CI 0.56 to 0.98). Rhino: 45.2% vs. 60.3%; unadjusted RR 0.75 (95% CI 0.55 to 1.02). LRTI: 41.1% vs. 51.0% unadjusted RR 0.81 (95% CI 0.53 to 1.03). Antibiotic within 28 days of index visit: Overall: 52.7% vs. 65.1%; adjusted[a] RR 0.81 (95% CI 0.62 to 0.99). Rhinosinusitis: 57.5% vs. 69.2% unadjusted RR 0.83 (95% CI 0.65 to 1.06). LRTI: 46.4% vs. 58.8% unadjusted RR 0.79 (95% CI 0.55 to 1.14).
	Diederichsen, 2000[68] Practice N=35 Provider N=35 Patient N=812 Adults, children; RTI Fair quality	January 1997- April 1997. Followup: 7 days.	Intervention: CRP testing during consultation. No strict guidelines for use of antibiotics. Control: usual care (clinical assessment only).	Frequency of antibiotic prescription: 43% (95% CI 40 to 47) vs. 46% (95% CI 43 to 50); adjusted[b] OR 0.9 (95% CI 0.70 to 1.20)
	Gonzales, 2011[80] Practice N=1 Provider N=NR Patients N=131 Adults (≥18 y); cough ≤21 days and one other acute RTI symptom Fair quality	November 2005 – March 2006. Followup: 2 to 4 weeks.	Interventions: *CRP testing + algorithm:* CRP testing and clinical management algorithm to guide chest x-ray and antibiotic treatment decisions. *Algorithm only:* Clinical management algorithm (without CRP testing) to guide chest x-ray and antibiotic treatment decisions.	Antibiotic treatment at index visit: CRP + Algorithm vs. Algorithm only: 37% (95% CI 26 to 48) vs. 31% (95% CI 19 to 43); unadjusted RR 1.23 (95% CI 0.77 to 2.00).
	Melbye, 1995[e180] Practice N=10 Patient N=239 Patients >18 y; "subjective complaint of: (a) pneumonia, bronchitis, or asthma, or with (b) cough, shortness of breath, or chest pain on deep inspiration". "Moderate risk of bias"	RCT (individual level). Followup: 21 days	Intervention: CRP testing at the end of consultation; algorithm to guide antibiotic prescribing based on duration of illness and recommended CRP cut-off values. Control: Usual care.	Antibiotic treatment at index visit: 50.0% vs. 51.9%; unadjusted RR 0.96 (95% CI 0.75 to 1.24). Antibiotic within 28 days of index visit: 56.5% vs. 59.5%; unadjusted RR 0.95 (95% CI 0.76 to 1.18).

Table 7. C-reactive protein point-of-care testing interventions (continued)

Study and Characteristics		Study Details	Intervention and Control Details	Outcomes
RCTs	Takemura, 2005[123] Practice N=1 Provider N=11 Patients N=301 Patients with fever (≥ 37.5° C) and suspected infection Fair quality	December 2000 – January 2003. Followup duration not reported.	Intervention: CRP + WBC testing at time of consultation. Clinical guidance not described; CRP reference level ≤ 5 mg/L. Control: usual care.	Antibiotics received: 57.5% vs. 91.0%; unadjusted RR 0.63 (95% CI 0.52 to 0.74)
Observational	Bjerrum, 2004[137] Practice N=367 Provider N=367 Patient N=1,444 Patients with acute sinusitis; median age, y (IQR)=40/41 (31 – 54) Fair quality	Observational November 2001 – January 2002. Followup: None.	Intervention: access to CRP testing. Control: no access to CRP testing.	Antibiotics prescribed: 59% vs. 78%; adjusted[d] OR 0.43 (95% CI 0.33 to 0.58)

CAP = community acquired pneumonia, CI = confidence interval, CRP = C-reactive protein, ED = emergency department, LRTI = lower respiratory tract infection, N = sample size, OR = odds ratio, RCT = randomized controlled trial, RR = relative risk, RTI = respiratory tract infection, URTI = upper respiratory tract infection, WBC = white blood cell

[a]Adjusted for clustering.

[b]Adjusted for age, clinical findings, and symptom duration.

[c]Adjusted for multiple factors, including clustering by physician and practice.

[d]Adjusted for patient sex, patient age, number of patients listed in practice, and clinician workload.

[e]As reported in Aabenhus, 2014[27].

Procalcitonin Point-of-Care Testing

Adults

We found a good-quality systematic review (in 2 publications) on the use of procalcitonin in assisting with diagnosis and treatment decisions for adults with a range of RTIs (Table 8).[23,24] Although the review included diagnoses that are not included here (e.g. community acquired pneumonia), and was primarily aimed at determining the value of procalcitonin by setting (primary care, ED, intensive care unit), subgroup analyses of four trials provide information relevant to this review on overall antibiotic prescribing (appropriate prescribing was not measured). In the review, two trials (one good and one fair quality) in the primary care setting assessed the use of procalcitonin in adults with upper or lower acute RTI.[52,54] Both used algorithms that suggested antibiotics were not necessary with procalcitonin levels <0.25 mcg/L, one study evaluated a single measurement at diagnosis,[54] and the other included a repeat measure 6−24 hours later in patients not given antibiotics.[52] The review finds that use of a procalcitonin algorithm for prescribing in the primary care setting led to fewer antibiotics being prescribed compared with no procalcitonin results (OR 0.1; 95% CI 0.07 to 0.14). The risk difference between the groups was 74 percent in one trial and 42 percent in the other. The trial with the largest difference in prescribing had a high incidence of antibiotic prescribing in the control group (97%). Nineteen percent of these patients had been diagnosed with a nonacute RTI infection such as CAP.[52] The other study had a lower prescribing rate in the control group, 36.7 percent, with 8 percent of patients having nonacute RTI diagnoses.[54] Both studies were conducted in European countries; therefore, applicability to the US setting is unclear. These studies provided moderate-strength evidence on overall antibiotic prescribing.

The review also conducted subgroup analyses of data from four trials (2 good, 2 fair)[52,54,63,119] to examine rates of prescribing for URTI and acute bronchitis separately, and found that both were reduced with the use of procalcitonin. The pooled absolute difference in prescribing was 33 percent for URTI (OR 0.14; 95% CI 0.09 to 0.22 and 0.15) and 42 percent for bronchitis (95% CI 0.10 to 0.23).[52,54,63,119]

Children

A single good-quality RCT of procalcitonin use in pediatric patients included children ages 1 to 18 presenting to two EDs in Switzerland with LRTIs, an adult procalcitonin algorithm was applied in one group and not the other (randomization at the patient level).[45] The study reports overall antibiotic prescribing. All patients also had CRP measurements taken and procalcitonin was measured again at day 3 and 5. Of children with a LRTI diagnosis other than CAP (36% of those enrolled), the difference in prescribing of antibiotics on day 1 was 21.7 percent more antibiotic prescribing in the procalcitonin group than the control group (RR 4.34; 95% CI 2.40 to 7.84; calculated for this report). This was low-strength evidence of greater overall antibiotic prescribing with use of procalcitonin as a point-of-care test in children.

Outcomes by Subgroups

Diagnostic Certainty. The use of a procalcitonin algorithm can be considered a method to improve the clinician's diagnostic certainty, or a measure of the clinician's perception of the patient's illness severity. The algorithms used in these studies were consistent in that a level of ≤25 mcg/L was considered to indicate that antibiotics were unlikely to be necessary, such that there was no variation in the use of this cutoff for "appropriate" use of antibiotics across the

studies to be evaluated, even if this is an indirect measure of appropriateness. Examination of specific decisions made by clinicians that deviated from the algorithm may have shed light on these questions. All four studies in adults reported greater than 70 percent compliance with the algorithm, and any impact of deviations from the algorithm based on clinician perception of individual patient illness severity couldn't be determined from these studies.

Age. The evidence currently available is distinctly different for adults and children. Procalcitonin was very effective in improving antibiotic use in adults with both upper and lower acute RTI, while there was an opposite effect in children. Although this finding is limited to a single study,[45] it was a good-quality study with adequate sample size to detect a difference of 15 percent between groups with a LRTI diagnosis other than CAP. In the adult studies, an effect was seen in primary care, as well as in subgroups based on diagnosis of URTI and acute bronchitis.

Table 8. Studies of effects of procalcitonin testing on appropriate antibiotic prescribing

Population	Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Children	Baer, 2013[45] Patient N=337 Provider N=NR Practice N=2 Children and adolescents, 1 mo. to 18 y Good quality	RCT January 2009 – February 2010	Intervention: procalcitonin-guided antibiotic treatment (initiation, continuation, or termination of antibiotic treatment strictly guided by procalcitonin cut-off levels). Control: clinically-guided standard care.	Antibiotic prescription within 14 days of randomization: N (%): 27 (45) vs. 10 (17) Rate difference (95% CI): 28 (12 to 43) OR (95% CI): 4.09 (1.80 to 9.93)
Adults	Schuetz, 2011[24] Schuetz, 2012[23] Good quality	Systematic Review RCT dates: range 2002 - 2008	Intervention: procalcitonin-guided approach to antibiotic therapy in patients with respiratory infections. Includes non-acute RTIs, with subgroup information on acute RTIs. Organized by setting. PCT level of ≤25 mcg/L interpreted as not requiring antibiotics. Control: standard approach to antibiotic therapy.	Initiation of antibiotics, PCT vs. Control Adjusted OR; 95% CI ARTI in Primary Care Setting: OR 0.1; 95% CI 0.07 to 0.14 Upper ARI: OR 0.14; 95% CI, 0.09 to 0.22 Acute bronchitis: OR 0.15; 95% CI, 0.10 to 0.23

CI = confidence interval, L = liter, LRTI = lower respiratory tract infection, mcg = microgram, mo. = month, N = sample size, OR = odds ratio, PCT = procalcitonin, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection, y = year

Viral Point-of-Care Testing

A good-quality systematic review of four trials,[49,69,83,111] five fair-quality RCTs, and one fair-quality observational study evaluated the utility of rapid viral testing in reducing overall antibiotic prescribing for acute RTI in adults, children, or a mixed population.[26,49,53,69,83,111,139] There was one additional study rated poor quality.[109] Low-strength evidence suggests a beneficial effect of multi-viral point-of-care testing in reducing overall antibiotic prescribing in adults, but that use of rapid influenza testing in children does not affect overall antibiotic prescribing. Evidence on the use of rapid influenza testing on overall antibiotic prescribing in a mixed age population, with more adults than children, was insufficient.

Adults

A fair-quality RCT of using a multi-viral reverse transcriptase polymerase chain reaction (PCR) point-of-care test with results being either available within 24 hours or in delayed fashion (8 or more days later) in adult patients with acute RTI found the proportion of patients prescribed antibiotics within 48 hours of initial visit was significantly lower in the patients assigned to point-of-care testing; 4.5 versus 12.3 percent (7.8% difference; $p<0.01$).[53] This test included 13 respiratory viruses (parainfluenza virus types 1 through 3, influenza viruses A and B, human metapneumovirus, respiratory syncytial virus, human rhinovirus, enterovirus, adenovirus, and human coronavirus types 229E, OC43, and NL63) and Mycoplasma pneumoniae and Chlamydophila pneumoniae. This evidence is low strength.

Children

In contrast, a good-quality systematic review[26] of four trials[49,69,83,111] of point-of-care testing specifically for influenza in children in the ED setting found no benefit in reducing overall antibiotic prescribing. The review reports that together, the four studies included a total of 759 children in viral point-of-care testing arms and 829 patients in comparator groups. Rates of antibiotic prescribing varied between 18 and 32 percent in viral point-of-care testing arms and 21 to 30 percent in comparator groups. While one reported a significant difference in the proportion of patients given antibiotics between physicians using point-of-care test results versus those in comparator arms (RR 0.66; 95% CI 0.45 to 0.96), the pooled estimate reported showed a mild and nonsignificant decrease in total antibiotic prescribing in the ED (RR 0.89; 95% CI 0.71 to 1.12). This evidence is moderate strength.

Mixed Populations

A retrospective observational study conducted using ED data on rapid influenza testing from the National Hospital Ambulatory Medical Care Survey evaluated three influenza seasons from 2007 to 2009 and included all age groups, with one-third being children ages 0−5 years.[139] In this study, rapid influenza testing resulted in fewer antibiotic prescriptions after diagnosis of influenza compared with no testing and a diagnosis of influenza (11% vs. 23%; $p=0.05$). It is important to note that this analysis is limited to those diagnosed with influenza but without chart review true appropriateness of antibiotic prescribing cannot be determined. The authors note that the number of patients in the referent group test positive and diagnosis positive was very small (N=30). This evidence was insufficient to draw conclusions.

Group A Beta Hemolytic Strep Point-of-Care Testing (Rapid Strep Tests)

Three fair-quality RCTs evaluated the utility of point-of-care testing using rapid strep tests compared with usual care or a clinical score.[97,101,132] All were conducted in the outpatient setting among primary care physicians (general practitioners, family practitioners, pediatricians); eligible patients had acute pharyngitis symptoms and one enrolled children, one enrolled both adults and older children, and one restricted to adults. Only one measured appropriateness of antibiotic prescribing, determined by throat culture; appropriate prescribing were cases with positive culture with antibiotics prescribed negative culture without antibiotics prescribed.[97] Two studies reported similar sensitivity (89.8% and 83.1%) and specificity (93.8% and 93.3%) for the tests.[97,101]

All three trials found that the rapid strep test decreased overall antibiotic prescribing for acute pharyngitis by 20 to 52 percent (Table 9). In the one study directly measuring appropriate antibiotic prescribing, the authors used a clinical score to determine “appropriateness.” The

proportion of patients appropriately prescribed antibiotics in the rapid strep test arm versus the standard care was 22.9 versus 6.0 percent, a statistically significant decrease of 16.9 percent.[97]

Outcomes by Subgroups

Location. One of the trials stratified the randomization of physician groups by practice location and found that the rapid strep test resulted in a much steeper drop in prescriptions among hospital-based clinicians compared to clinicians in private practice.[101]

Age. None of the studies suggested differential effectiveness based on age of the patient.

Table 9. Randomized controlled trials of point-of-care rapid strep testing compared with usual care or clinical score

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Maltezou, 2008[101] Greece Patient N=820 Provider N=24 Children (2−14 y); pharyngitis Fair quality	Group RCT December 2005 – June 2006 and September 2006 – June 2007	Intervention: 1) Private practice pediatricians Rapid strep test and culture. 2) Hospital-affiliated pediatricians Rapid strep test and culture. Control: Private practice pediatricians' usual care.	Control vs. Intervention in private practice and vs. hospital-based % Antibiotic prescribed: 72.2% vs. 33.7% vs. 19.8%, p=0.004
Worrall, 2007[132] Newfoundland Patient N=533 Provider N=40 Adults; acute sore throat Fair quality	Cluster RCT February, March, and April 2005	Intervention: 1) Sore throat decision rules only 2) Rapid strep test. 3) Sore throat decision rules and rapid strep test. Control: Usual care.	Usual Care vs. Rapid test only % of Visits Where Antibiotics Were Prescribed: 58.2 vs. 26.7; p<0.001
Llor, 2011[97] Patient N=543 Practice N=20 Patients (14−60 y); acute pharyngitis Fair quality	Cluster RCT January to May 2008	Intervention: Rapid strep test. Control: Usual care. (Cultures taken in both groups.)	Intervention group vs. Control Inappropriateness of antibiotic prescription according to culture: 26.9% vs. 60.0%; p<0.001 Prescription of antibiotics 43.8 % vs. 64.1%; p<0.001

N = sample size, p = p-value, RCT = randomized controlled trial, y = years.

Decision Rules

One small fair-quality RCT provided insufficient evidence to draw conclusions about its comparison to usual care. Use of a clinical decision rule alone did not statistically significantly reduce family physicians' antibiotic prescriptions for sore throat (55% vs. 58% p=NS).[132] The sore throat decision rule used in the study required antibiotic prescription when physicians rated patients as having met at least three of the following criteria: (1) no cough, (2) fever above 38 degrees Celsius, (3) swollen submandibular glands, and (4) exudate on throat or tonsils.

Tympanometry

In a fair-quality RCT of 398 children ages 6 to 36 months with suspected AOM, all children underwent tympanometry with results made available to treating physicians in one group and not for the other group.[121] While all physicians in the group received information on interpreting tympanometry results, 59 percent had or were receiving specific training in a fellowship program. Less than 1 percent of patients had unsuccessful tympanometry. This study provided low-strength evidence that 28 percent of the children received a prescription for an antibiotic, with no differences between groups (28.8% with tympanometry results vs. 26.8% without;

p=0.62). Serious AOM was diagnosed in 5.8 percent with tympanometry results and 3.2 percent in the group without these results. Based on physician report, having the tympanometry results available altered the decision to prescribe antibiotics in only 2.8 percent of cases.

System-Level Interventions

Decision Support

Five fair-quality RCTs[67,81,88,89,103] and three observational studies[159,161,165] assessed electronic decision support systems as a method to improve antibiotic prescribing for acute RTIs. Two other RCTs rated poor quality and were excluded (Appendix E).[75,104] The studies involved intervention groups that received electronic clinical decisionmaking tools compared with no decision support, except one study that also studied a paper decision support system (Table 10).[81] All studies reported comparison of overall antibiotic prescribing between intervention and comparator group but two compared the change in antibiotic prescribing before and after study periods.[67,81] With regard to patient characteristics, one was limited to acute bronchitis among older children and adults,[81] one involved children and adults with acute pharyngitis,[103] one included children and studied a variety of conditions, and the remaining two included any patient with clinical visits for acute RTI.[88,89]

Overall Prescribing

Three studies measured overall antibiotic prescribing,[88,89,103] although two reported "appropriate" antibiotic prescribing as a secondary outcome (see below).[88,89] These studies provide moderate-strength evidence that when the systems were used at least 50% of the time, overall antibiotic prescribing was reduced. For example, in the study reporting the highest level of use of the electronic support system (57%) a significant reduction was found. (−9.2%; RR 0.73; 95% CI 0.58 to 0.92)[94] In contrast, when the systems are used infrequently there is no impact. Two studies that were conducted in the same population by the same group of researchers, where use of the system was only 6 or 28 percent they failed to show any difference in antibiotic prescribing associated with an electronic intervention in patients with more broadly defined acute RTI (reduction of 0% to 4%).[88,89] However, in per-protocol analyses limited to instances where the intervention tool was used, some small reductions in antibiotic prescribing were noted. For example, Linder, et al. performed a secondary analysis comparing users and nonusers of an electronic decision support tool, and found a small decrease in antibiotic prescribing overall for acute respiratory infections of all types (42% among users vs. 50% among nonusers, p=0.020).[88] Taken together, these studies suggested that use of electronic decision-support can have some effect upon prescribing practice if physicians use them (Table 10). The observational evidence did not provide better evidence or fill gaps in the trial evidence; one found the intervention unsustainable and two found benefit although small.[159,161,165]

Appropriate Prescribing

Two studies assessed appropriate prescribing; one defined appropriate antibiotic prescribing based on patients with ICD-9 codes for acute bronchitis and then limited to patients ages 13 to 64 years without presence of comorbidities and without antibiotic "responsive" secondary conditions including pharyngitis, sinusitis, AOM, and pneumonia. It is presumed that identification of these conditions was also based on ICD-9 codes alone, not chart review.[81] The other presented clinicians with evidence guiding prescribing in response to the electronic prescription initially entered. Following the evidence-based recommendation was considered

appropriate prescribing.[67] These studies provide moderate-strength evidence that the electronic decision support systems improved appropriate antibiotic prescribing, as defined in these studies (Table 10). In the study of patients with acute bronchitis, electronic decision support led to a greater improvement in appropriate antibiotic prescribing compared with control (13% difference; p=0.01) and a paper decision support tool (6% difference), although the difference between electronic and paper was not statistically significant.[81] The other study found that for AOM electronic support via presenting evidence in reaction to initial prescribing resulted in a 24 percent decrease in prescribing of antibiotics against the evidence-based recommendation.[67] As noted in Table 10, the use of the electronic systems was reported as 100 percent in one study and not reported in the other. The consistency and precision of these fair-quality studies support a moderate-strength evidence of a beneficial effect in improving appropriate prescribing.

Table 10. Studies of electronic decision support and antibiotic prescribing

Prescribing Pattern	Study and Characteristics	Design and Dates	Intervention and Control Details	Percent Use of System	Outcome
Overall Prescribing	Linder, 2009[89] Patient N=111,820 Provider N=443 Acute RTI (undefined) Fair quality	Cluster RCT November 3, 2005 – May 31, 2006	Intervention: EHR-integrated, documentation-based clinical decision support system for the care of patients with ARIs ("ARI Smart Form"). Control: usual care (no decision tool).	6%	% Visits with antibiotic prescribing Control vs. intervention: 39% vs. 43% OR 0.8 (95% CI 0.6 to 1.2)
	Linder, 2010[88] Patient N=136,633 Provider N=573 Pharyngitis, sinusitis, AOM, influenza, acute bronchitis, nonspecific upper respiratory infection Fair quality	Cluster RCT November 27, 2006 – August 31, 2007	Intervention: EHR-based feedback system ("ARI Quality Dashboard"). Control: usual care (no decision tool).	28% at least once	% Visits with antibiotic prescribing Control vs. intervention: 47% vs. 47%
	McGinn, 2013[103] Patient N=1,172 Provider N=168 Pharyngitis or respiratory infection Fair quality	RCT November 1, 2010 – October 31, 2011	Intervention: Walsh and Heckerling clinical prediction rules; EHR integrated; 1-hour in-person training. Control: usual care + background information on Walsh and Heckerling clinical prediction rules.	57%	% Visits with antibiotic prescribing Control vs. intervention: 29.2 vs. 38.4% (−9.2%); RR 0.73 (95% CI 0.58 to 0.92)

Table 10. Studies of electronic decision support and antibiotic prescribing (continued)

Prescribing Pattern	Study and Characteristics	Design and Dates	Intervention and Control Details	Percent Use of System	Outcome
Appropriate Prescribing	Davis, 2007[67] Patient N=12,195 (visits) Provider N=44 AOM Fair quality	Cluster RCT November 1999 – December 2003 (PCC) and June 2002 – December 2003 (SP)	Intervention: evidence-based message system presenting real-time evidence to providers based on prescribing practices. Control: no message system.	100%	% Prescribing according to evidence Change in control vs. intervention (adjusted) AOM: 24% (8%, 40%)
	Gonzales, 2013[81] Patient N=NA Provider N=NR Practice N=33 PCP sites Acute bronchitis Fair quality	Cluster RCT October 1, 2009 – March 31, 2010 (winter period following intervention, compared to previous 3 winter periods)	Intervention: *Printed decision support*: support for acute cough illness through print-based strategy. *Computer-assisted decision support*: decision support through an electronic medical record-based strategy. Control: no support.	NR	Change in antibiotic prescribing (%) Control: 72.5% vs. 74.3% Printed decision support: 80% vs. 68.3% Electronic decision support: 74% to 60.7%. Control vs. printed support: p=0.003 Control vs. computer support: p=0.01 Printed vs. computer support: p=0.67

AOM = acute otitis media, CI = confidence interval, N = sample size, NA = not applicable, NR = not reported, OR = odds ratio, p = p-value, PCP = primary care practice, RCT = randomized controlled trial, RR = relative risk

[a] Two poor-quality studies not listed above.

Multifaceted Interventions

Combining Multiple Types of Behavioral Interventions Versus No Intervention

Two fair-quality trials and seven observational studies (six fair-quality and one poor-quality) provided low-strength evidence on the effectiveness of three or more types of interventions on antibiotic prescribing for acute RTI. Five studies included a component of provider education in addition to audit and feedback about prescribing practices. Additional elements of the interventions included provider communication training,[129,171] a clinical decision support tool,[154] patient education,[143,145-147] or introduction of clinical algorithms.[167]

Overall Prescribing

Clinician Education Plus Audit and Feedback

There was low-strength evidence that multifaceted interventions that combine provider education and audit and feedback components do not statistically significantly reduce overall antibiotic prescribing for children with acute RTI. This evidence came from a fair-quality RCT[77] and a fair-quality observational study,[141] both in children with acute RTI (Table 11). The combination of (1) provider education with World Health Organization (WHO) standard treatment guidelines and (2) auditing with scoring led to a trend toward improvement in overall antibiotic prescriptions of 8.5 percent when implemented in Bangladesh in clinics with baseline antibiotic prescription rates of 86 to 90 percent.[141] In the more recent RCT conducted in the United States, a combination of (1) 1-hour on-site clinician education session and (2) 1-year of personalized, quarterly audit and feedback only led to a 0.2 percent reduction of antibiotic prescribing, which was smaller than the 1.7 percent reduction seen in the control group. At 6 to 8 percent, baseline antibiotic prescribing rates were already very low in this study population.

Patient and Clinician Education Plus Audit and Feedback

In a series of related observational studies,[143,145,146] the combination of (1) physician education, (2) patient education, and practice profiling (audit and feedback) proved more effective than usual care in reducing overall antibiotic prescribing in adults with bronchitis, but not for other RTIs,[143,146] and also not for various RTIs in the elderly[145] or in children with acute pharyngitis.[143] Compared with a limited intervention group that only received office-based patient education materials, the reduction in overall antibiotic prescriptions for the full multifaceted intervention was also significantly greater in adults with bronchitis, but not other RTIs.[146]

Peer Academic Detailing (Education, Encouraging Delayed Prescribing, and Audit and Feedback)

There was insufficient evidence to determine whether a multifaceted intervention with two visits from peer academic detailers covering (1) provider education on guidelines, (2) encouragement of delayed prescribing, and (3) personalized audit and feedback improves overall antibiotic prescribing over usual care in patients with acute RTI. The Norwegian general practice Rx-PAD study (prescription peer academic detailing) was a fair-quality RCT that compared the 3-component intervention as used to reduce (1) antibiotics and (2) anticholinergic effects, long

acting benzodiazepines, muscle relaxants, strong analgesics, theophylline, combinations of different cardiovascular drugs, non-steroidal anti-inflammatory drugs in combinations, and three or more concurrent psychotropic drugs.[79] As this comparison was not relevant to this review, the only useful evidence from that study was the before after comparison in the antibiotic group. Although there was a small statistically significant reduction in overall prescriptions since we didn't have a relevant control group to compare it to, we cannot rule out that the change was a function of a temporal trend.

Patient and Clinician Education Plus Communication Training Plus Audit and Feedback

Based on two related studies, one RCT[129] and one observational study,[171] of a combination of (1) education meetings for providers, assistants and pharmacists, (2) communication training, (3) monitoring and feedback on prescribing behavior, and (4) patient education materials for patients with acute RTI in the Netherlands there was low-strength evidence that the multifaceted intervention may statistically significantly reduce overall antibiotic prescriptions for some infection types. Although the RCT found a statistically significant 12 percent reduction in overall antibiotic prescribing, the related observational study that used the same set of interventions did not show an effect.[171] Authors attributed this difference to less rigorous application of the intervention in the observational study than in the trial. Ultimately, this may more accurately reflect the difficulties in applying a multifaceted intervention in a real world setting.

Appropriate Prescribing

Clinician Education Plus a Clinical Algorithm

There was insufficient evidence that a multifaceted intervention that combined multiple clinician education components can increase appropriate prescribing in patients with acute RTI. A fair-quality, before-after study conducted in Mexico directly measured the appropriate prescribing of antibiotics based on application of a clinical guideline in accordance with specific, predefined criteria.[167] The intervention involved use of a clinical algorithm and a three-part educational intervention for physicians including interactive workshops, individual tutorials, and round-table peer-review sessions led by trained clinical tutors.[167] Baseline inappropriate prescribing was 78 percent. Compared with baseline, the average increase in appropriate prescribing of antibiotics for the combined intervention was statistically significant while the control group did not show changes (difference in mean proportions: 23; 95% CI 10 to 35 vs. 1.5; 95% CI −8.6 to 12, $p<0.05$). This evidence is insufficient because of the lack of a control group, in addition to unknown consistency.

Electronic Decision Support Plus Patient Education Plus Delayed Prescribing Plus Audit and Feedback

Appropriate prescribing (as defined by CDC guidelines) was also directly measured in a fair-quality before-after study of a more intense multifaceted intervention, ABX-TRIP (The Reducing Inappropriate Prescribing of Antibiotics by Primary Care Clinicians), which combined (1) electronic decision support with local tailoring and extensive site-based training, (2) audit and feedback, (3) delayed prescribing encouragement; and (4) patient education materials.[154] This was a demonstration project involving nine primary care practices in nine states that are in a practice-based research network (PPRNet), whose members use a common electronic health record. Baseline inappropriate antibiotics prescribing was 41 percent for adults and 21 percent for children and was not significantly improved by the multifaceted intervention in either group

(Table 11). The electronic decision support system was only used at 6 percent of the documented encounters, limiting the assessment of the intervention efficacy. This evidence is insufficient to draw conclusions.

Outcomes by Subgroups

Studies on multifaceted interventions provide only limited information about subgroup effects. Only studies of one multifaceted intervention reported their own subgroup analyses, which provided some evidence that the effectiveness of the combination of (1) physician education (2) practice profiling, (3) academic detailing, and (4) patient education varies by type of RTI and age and is greatest in adults with bronchitis.[143,145-147]

Age

In adults, the multifaceted intervention reduced overall antibiotic prescribing for bronchitis, but not uncomplicated sinusitis,[146] however in the elderly, the intervention did not significantly reduce overall antibiotic prescribing in bronchitis or sinusitis. The intervention also did not reduce overall antibiotic prescribing in children with acute pharyngitis. This may be attributed to the prevalence of certain bacteria in the pediatric population, clarity on general clinical recommendations and factors other than patient expectations and demands affecting antibiotic treatment decisions in the elderly.

Table 11. Studies of multifaceted interventions compared with usual care

Prescribing Pattern	Study and Characteristics	Design and Dates	Infection or Diagnosis	Intervention and Control Details	Outcomes
Overall Prescriptions	Gerber, 2013[77] Patient N=185,212 Provider N=162 Practice N=18 Fair quality	RCT October 2008-June 2011	Acute RTI in children	Intervention: (1) 1-hour on-site clinician education session (June 2010) followed by (2) 1 year of personalized, quarterly audit and feedback of prescribing for bacterial and viral URTIs. Control: usual practice.	Any antibiotic prescribing for viral infections, % before, after, absolute change: Intervention: 7.9%, 7.7%, −0.2% Control: 6.4%, 4.5%, −1.9% Difference of differences: −1.7%; p=0.93
	Chowdhury, 2007[141] Practice N=60 Children <5 Fair quality	Observational Study period NR	Acute RTI in children under 5 years	Intervention: (1) Provider education with WHO standard treatment guidelines, (2) auditing with scoring. Control: no intervention.	Antibiotic prescribing; pre vs. post, absolute difference Intervention: 90.3% vs. 66.6%, −23.7%, p<0.05 for 6/8 sites, p=NR overall Control: 85.9% to 70.7%, −15.2%, p<0.05 for 4/8 sites, p=NR overall Difference of differences: 8.5%
	Gonzales, 1999[146] Patient N=4,489 Provider N=93 Practice N=4 Fair quality	Observational	Various RTI	Intervention: (1) Physician education, (2) practice profiling (audit and feedback), (3) and patient education. Control: local control and distant control groups.	Antibiotic Prescribing Rates *Uncomplicated Acute Bronchitis* Full intervention:−26%; 74 vs. 48, 0.003 Control: −2%; 78 vs. 76, 0.81 *Uncomplicated URTIs:* No difference, p>0.05 *Uncomplicated sinusitis*: +2% vs. 0%; No difference, p=0.81
	Gonzales, 2004[145] Patient N=4,270 patient visits Provider N=NR Practice N=55 (4 intervention, 51 control) Fair quality	Observational	Various RTI in elderly	Intervention: (1) Physician education, (2) practice profiling (audit and feedback), (3) and patient education. Control: local control and distant control groups.	Antibiotic Prescription Rates (%) mean change before/after for intervention vs. control: Bronchitis: −8 vs. −3 Sinusitis: −9 vs. −2 URTI: +1 vs. +1

Table 11. Studies of multifaceted interventions compared with usual care (continued)

Prescribing Pattern	Study and Characteristics	Design and Dates	Infection or Diagnosis	Intervention and Control Details	Outcomes
Overall Prescriptions	Gonzales, 2005[143] Patient N=16,686 baseline, 14,648 study period Provider N=1,629 baseline, 1,193 study period Practice N=709 baseline, 592 study period Fair quality	Observational	Various RTI	Intervention: (1) Physician education, (2) practice profiling (audit and feedback), (3) and patient education. Control: local control and distant control groups.	Adjusted Antibiotic Prescription Rates % change before-after for intervention vs. distal control vs. local control: Children with Acute Pharyngitis: −4% vs. +1 vs. −2; NSD Adults with bronchitis: −24%, p<0.002 vs. −7% to −10%, p=0.006
	Gjelstad, 2013[79] Rx-PAD Patient N=NR Provider N=382 (79 groups) Fair quality	Before-After 2005 – 2006	Patients with acute RTOs	Intervention: (1) Provider education; (2) delayed prescribing encouraged; (3) peer academic detailing. Control: aforementioned intervention applied to general prescribing in patients >70 y (excluding antibiotics)	Preintervention: 31.7% Postintervention: 30.4% Change: −1.29 (95% CI −2.43 to −0.16)
	Welschen, 2004[129] Patient N=3,620 Provider N=89 GPs (12 groups) Fair quality	RCT 2001 – 2002	RTI	Intervention: (1) Education meetings for providers, assistants and pharmacists, (2) communication training, (3) Monitoring and feedback on prescribing behavior, (4) patient education materials. Control: No intervention.	Antibiotic prescription rates, % change −4 vs. +8 ; Mean difference of changes (95% CI): −12 (−18.9 to - 4.0) −10.7; (−20.3 to −1.0) Changes in mean number of antibiotic prescriptions per 1000 patients (I vs. C) - 9.7 (p=0.05) vs. + 1.9 (p=0.6)

Table 11. Studies of multifaceted interventions compared with usual care (continued)

Prescribing Pattern	Study and Characteristics	Design and Dates	Infection or Diagnosis	Intervention and Control Details	Outcomes
Overall Prescriptions	Smeets, 2009[171] Patient N=NR Provider N=382 providers (25 groups) Practice N=141 Fair quality	Observational 2005 – 2007	RTI	Intervention: (1) Education meetings for providers, assistants and pharmacists, (2) communication training, (3) Monitoring and feedback on prescribing behavior, (4) patient education materials. Control: No intervention.	Antibiotic prescriptions/1000 patients 2005: +12% vs. +15% (NS) 2007: +13% vs. +12% (NS)
Appropriate Prescribing	Litvin, 2013[154] Provider N=39 Fair quality	Before-After 1/10−3/11, 7/11−3/12	Acute RTI	Intervention: (1) Electronic health records-based electronic decision support with local tailoring and extensive multi-phase, site-based training, (2) Audit and feedback, (3) Delayed prescribing encouragement, (4) Patient education materials. Control: Pre-intervention	Inappropriate antibiotic prescribing: Adults: +1.6% (95% CI −5.4 to 8.5) Children: −1.9% (95% CI −9.0 to 5.3)
	Reyes-Morales, 2009[167] Patient N=1495 Provider N=106 Fair quality	Controlled Before-After	Acute RTI	Intervention: (1) Clinical algorithm, (2) clinical tutors trained, (3) three-part educational intervention for physicians included interactive workshops, individual tutorials, round-table peer-review sessions. Control: Preintervention.	Appropriate prescription of antibiotics (difference of mean proportions vs. baseline, 95% CI): Workshop: 14 (2.6 to 26) vs. −1.2 (−11 to 8.3) Tutorial: 11 (−0.7 to 23) vs. −4.4 (−14 to 5.3) Peer review: 23 (10 to 35)* vs. 1.5 (−8.6 to 12); p<0.05 vs. control

CI = confidence interval, GP = general practitioner, N = sample size, NR = not reported, NS = not significant, NSD = no significant difference, p = p-value, RCT = randomized controlled trial, RTI = respiratory tract infection, URTI = upper respiratory tract infection, WHO = World Health Organization

Point-of-Care Tests Combined With Other Strategies

CRP Combined With Provider-Focused Communication Training

Two fair-quality RCTs provided moderate-strength evidence that the combination of training in enhanced provider communication plus use of CRP testing statistically significantly reduces overall antibiotic prescribing compared with usual care and communication training alone, but likely not compared with CRP testing alone. The Improving Management of Patients with Acute Cough by C-reactive Protein Point of Care Testing and Communication Training (IMPAC^{3}T) trial involved 20 general practices in the Netherlands and focused on adults who consulted for LRTI with the primary symptom of cough during the winters of 2005 to 2006 and 2006 to 2007.[56] The communication skills intervention involved a 2-hour, face-to-face small group training seminar, preceded and followed by simulated clinical encounters and peer review of colleagues' simulation transcripts. In contrast, the objective of the consortium-supported study (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe [GRACE]) was to assess wider effects of the interventions by targeting a more broad base of patients with both upper and LRTIs who were seen between February and March of 2011 across 259 primary care practices in six European countries.[95] The communication training was internet-based and accompanied by video demonstrations of consultation techniques and an interactive booklet to use during consultations, which the authors suggested may have the potential advantages of accommodating more wide dissemination without requiring on-site highly trained facilitators. Based on our pooled analysis, overall antibiotic prescribing rate was 31 percent in the combination group, which was statistically significantly lower than in the usual care group (59%; OR 0.30; 95% CI 0.26 to 0.36) and in the group that only received communication training (40%; OR 0.67; 95% CI 0.56 to 0.78). There was heterogeneity between trials, however, in the comparison between the combination group and the group who received CRP testing alone. In the smaller, earlier IMPAC^{3}T trial, which was limited to patients with LRTI from the Netherlands, the combination intervention statistically significantly reduced overall prescribing rates compared with CRP testing alone (23% vs. 39%; OR 0.47; 95% CI 0.25 to 0.86), but not in the later, larger, multinational trial of patients with upper and LRTI that used an internet-based method of training delivery (32% vs. 35%; OR 0.87; 95% CI 0.72 to 1.04). The particular reason(s) for the heterogeneity was unclear as there is variation between these studies on multiple clinical and methodological factors.

Provider and Patient Education Combined With CRP

There was low-strength evidence, based on seven fair-quality observational studies that, compared with usual care, a multifaceted intervention that combines provider and patient education with use of CRP testing leads to a statistically significant reduction in overall antibiotic prescribing across various infection types compared with provider and patient education alone or control.[136,138,155-158] This evidence came from HAPPY AUDIT studies (Health Alliance for Prudent Prescribing, Yield And Use of Anti-microbial Drugs In the Treatment of Respiratory Tract Infections) involving general practitioners from Spain during the winters of 2002 to 2003[136] and from Denmark, Sweden, Lithuania, Russia, Spain, and Argentina in 2008 and 2009.[138,155,156,158] Two types of interventions were tested; patient and provider education combined with education on rapid tests in general and access to CRP specifically, compared with combined patient and provider education alone.

The first study reported overall prescription rates before and after the CRP+education intervention and for a control group in patients with URTIs and LRTIs seen in Spain during the

winters of 2002 to 2003 and evaluated variation across subgroups based on the infection categories of ears, tonsils, pharynx/larynx/trachea, sinuses, and bronchi/lungs,[136] while a later study by this same group evaluated whether changes in prescription rates before and after the CRP+education intervention vary across the countries of Denmark, Sweden, Lithuania, Russia, Spain, and Argentina.[138] Four other studies by another group of researchers reported the changes in overall prescription rates before and after the CRP+education and education-only interventions[157] and in a control group in patients with pharyngitis,[156] rhinosinusitis,[155] and LRTIs.[158] The study of patients with lower respiratory infections also evaluated subgroups of those with acute bronchitis.[158]

The magnitude of reductions in antibiotic prescriptions varied across infection types and the pattern of variation differed between observation periods of 2004 to 2005 and 2008 to 2009 (Table 12). In the study of 2004 to 2005, the greatest reductions with the CRP+education intervention were for pharynx/larynx/trachea and bronchi/lungs subgroups.[136] In contrast, for patients seen in Spain from 2008 to 2009, rhinosinusitis was consistently among the top two infection types that had the greatest potential for benefitting from the CRP+education intervention, compared with either usual care or the education-only intervention. For all acute RTI diagnoses, antibiotic prescribing was reduced more with the CRP+education intervention (OR 0.50; 95% CI 0.44 to 0.57) than with the education-only intervention (OR 0.99; 95% CI 0.89 to 1.10; $p<0.001$).[157] The reduction in antibiotic prescribing with the CRP+education intervention was greatest with influenza, the common cold, acute pharyngitis, acute tonsillitis, and acute bronchitis, while the education-only intervention resulted in increased prescribing for the common cold. In an earlier study, patients with ear infections[136] benefitted the least from the CRP+education intervention. The magnitude of the reductions in antibiotic prescriptions for URTIs and LRTIs with the CRP+education intervention, respectively, also varied between countries, with the largest seen in Lithuania (20% and 42%) and Russia (15% and 25%), then Spain (9% and 25%), Argentina (5% and 9%), Sweden (+5% and 5%), and Denmark (0% and 2%).[138]

Table 12. Comparison of overall antibiotic prescription rates from Happy Audit studies: Proportions of patients

Infection Type (N) Study Period, Location	Education + CRP vs. Usual Care[a] OR (95% CI)	Education alone vs. Usual Care[a] OR (95% CI)	Education + CRP vs. Education Alone[a] OR (95% CI)
Any acute RTI (N=10,312) 2008 – 2009 in Spain[157]	Any acute RTI: 0.50 (0.44−0.57) Common cold: 0.03 (0.01−0.06) Otitis: 0.48 (0.12−2.0) Sinusitis: 0.57 (0.18−1.8) Pharyngitis: 0.15 (0.09−0.25) Tonsillitis: 0.18 (0.09−0.37) Acute bronchitis: 0.31 (0.20−0.47) Influenza: 0.01 (0.00−0.07)	Any acute RTI: 0.99 (0.89−1.1) Common cold: 4.6 (2.4−8.9) Otitis: 1.3 (0.39−4.3) Sinusitis: 0.43 (0.14−1.3) Pharyngitis: 1.0 (0.68−1.6) Tonsillitis: 1.0 (0.58−1.9) Acute bronchitis: 0.61 (0.42−0.88) Influenza: 2.0 (0.60−6.5)	NR
Rhinosinusitis (N=380), 2008 – 2009 in Spain [155]	57% vs. 87%; 0.12 (0.01 to 0.32)	83% vs. 87%; 0.65 (0.21 to 1.01)	57% vs. 83%; 0.27 (0.15 to 0.49)
LRTI (N=2,150), 2008 – 2009 in Spain[158]	Overall: 44% vs. 77%; 0.21 (0.12 to 0.38) Bronchitis: 30% vs. 71%; 0.18 (0.13 to 0.23)	Overall: 56% vs. 77%; 0.42 (0.22 to 0.82) Bronchitis: 41% vs. 71%; 0.28 (0.21 to 0.39)	Overall: 44% vs. 56%; 0.61 (0.50 to 0.74) Bronchitis (N=1469): 30% vs. 41%; 0.63 (0.49 to 0.80)
Pharyngitis (N=3,646), 2008 – 2009 in Spain[156]	22% vs. 50%; 0.23 (0.11 to 0.47)	47% vs. 50%; 0.53 (0.23 to 1.2)	22% vs. 47%; 0.32 (0.28 to 0.37)
URTI and LRTI (N=4,136), Winter of 2004 – 2005 in Spain[136]	Overall: 24% vs. 32%; 0.67 (0.58 to 0.77) Pharynx/larynx/trachea (N=915): 8% vs. 18%; 0.40 (0.24 to 0.62) Bronchi/lungs (N=1,300): 40% vs. 61%; 0.43 (0.34 to 0.54) Tonsils (N=228): 49% vs. 68%; 0.45 (0.25 to 0.85) Sinuses (N=124): 49% vs. 61%; 0.61 (0.28 to 1.36) Ears (N=262): 42% vs. 25%; 2.17 (1.06 to 4.49)	NA	NA

CI = confidence interval, LRTI = lower respiratory tract infection, N = sample size, NA = not applicable, RTI = respiratory tract infection, URTI = upper respiratory tract infection

[a] Postintervention rates.

Rapid Strep Testing Combined With a Decision Rule

There was low-strength evidence from two fair-quality RCTs that a rapid strep test plus a decision rule can achieve a greater reduction in overall antibiotic prescribing for sore throat than usual care and delayed prescribing, but not the rapid strep test alone and moderate-strength evidence that the combination is better than the decision rule alone.[91,132] The first RCT involved 37 family doctors in eastern Newfoundland and enrolled 533 patients who were seen for sore throat during February to April of 2005. The decision rule in this study involved scoring patients with one point for each of the absence of cough, fever >38 degrees Celsius, swollen submandibular glands, and exudate on throat or tonsils. Scores of 3 to 4 indicated that antibiotics

were required. This RCT compared the rapid strep test plus the decision rule to usual care, the rapid strep test only, and the decision rule only. The second RCT involved 48 general practitioners and triage practice nurses in general practices in south and central England who saw people ages ≥3 presenting with acute sore throat (2 weeks or less of sore throat) and an abnormal looking throat (e.g., erythema and/or pus) between October 2008 and April 2011.[91] The clinical score used was FeverPAIN, which involved offering immediate antibiotics for score ≥4, delayed antibiotics for scores of 2 to 3, and no antibiotics for scores of 0 to 1. This RCT compared the RADT and decision rule combination to the decision rule only and delayed prescribing. The delayed prescription strategy was to leave the prescription for collection after 3 to 5 days. Findings across the two studies indicated that the combination of rapid strep test plus a clinical score led to significantly lower overall antibiotic prescribing rates compared with usual care (38% vs. 58%; RR 0.66; 95% CI 0.49 to 0.86),[132] the clinical score alone (EPC pooled rates: 36% vs. 47%; EPC-calculated pooled OR 0.70; 95% CI 0.50 to 0.98), and delayed prescribing (35% vs. 46%; RR 0.73; 95% CI 0.52 to 0.98),[91] but not the rapid strep test alone (38% vs. 27%; RR 1.43; 95% CI 0.98 to 2.11).[132] Absolute differences in rates were 10 to 11 percent for all comparisons.

Augmentation of Interventions

The second type of multifaceted intervention strategies assessed were those that can be considered augmentation of a primary intervention by adding a second intervention from a different category (e.g., education combined with system-level intervention). Six trials (five fair and one good quality in six publications) provided evidence on whether augmenting one intervention type with a second intervention affects antibiotic prescribing practices (Table 13).[51,94,95,98,108,117] Four reported on overall antibiotic prescribing while two measured appropriate prescribing. One assessed appropriate prescribing of antibiotics based on the following categories: (1) "never indicated" (acute bronchitis and colds/upper RTI); (2) "sometimes indicated" (sinusitis and uncharacterized AOM or pharyngitis); and (3) "always indicated" (streptococcal pharyngitis, AOM, and pneumonia).[117] Categorization was based on chart review and corroboration of clinician diagnoses. The other study defined appropriate prescribing as that which adhered to guidelines developed by the investigators, derived from evidence-based US guidelines endorsed in 2001 by the Centers of Disease Control and Prevention (CDC), the American Academy of Family Physicians, the American College of Physicians, and the Infectious Disease Society of America. In three trials, appropriate prescribing of antibiotics was indirectly measured as it was based mainly on prescribing of antibiotics after a specific period of time following the onset of symptoms.[94,98,108]

A fair-quality RCT provided moderate-strength evidence that adding clinical decision support to community education about antibiotic prescribing in children with acute RTIs in rural primary care settings is effective in improving appropriate prescribing and overall prescribing (Table 13).[117] The combined intervention resulted in a 27 percent lower rate of prescribing for the category of diagnoses where antibiotics were "never indicated" (p=0.03) compared with the community education strategy alone. In contrast, a second trial provided low-strength evidence that the addition of communication training for clinicians to clinician education does not improve the rate of appropriate prescribing, according to guidelines (Table 13).[51] This study also found no difference between these groups in the rate of overall prescribing for acute RTI.

For the outcome of overall prescribing, two trials assessed the benefit of adding minimal patient education to delayed prescribing techniques with conflicting findings (insufficient evidence).[94,98,108] In a factorial design RCT (N=807), the addition of a patient educational leaflet

to immediate, no, or delayed prescribing for acute illness with cough did not have a significant effect on patient-reported antibiotic use (p=0.58).[94,108] In contrast, an earlier RCT (N=259) that provided information leaflets to patients in addition to suggested delayed prescribing for acute bronchitis had a significant reduction in antibiotic usage among patients who received the leaflet compared with those who did not (difference 15%).[98] In the first study, patients in the delayed prescription group were required to return to clinic to retrieve the prescription if they felt they needed it after 14 days. Possibly as a result of the added hurdle of returning to clinic to retrieve the prescription, the overall rates of antibiotic use were very low (14%). In the second study, all patients were given a prescription to take home and decide if they needed it and the rate of filling the prescription were much higher (47% vs. 62% in intervention and control groups). These differences may explain the inconsistency of findings.

A fair-quality, multinational, cluster RCT provided low-strength evidence that combined internet training of primary care providers in use of CRP and communication skills resulted in reductions in antibiotic prescribing for acute RTI compared with communication training alone (32% vs. 41%; p<0.0001), but that the combination was not superior to CRP training alone (32% vs. 35%; p=0.11).[95]

Outcomes by Subgroups

Diagnosis

One study reported on diagnosis subgroup differences in overall prescription of antibiotics and prescription according to guidelines but the number of events was too low to draw conclusions.[51] In this study, communication training in conjunction with guideline education – compared with guideline education alone – was not associated with any statistically significant differences in overall prescribing for rhinosinusitis (21% vs. 38%; RR 0.56; 95% CI 0.27 to 1.16), exudative tonsillitis (65% vs. 67%; RR 0.97; 95% CI 0.54 to 1.73), or bronchitis (24% vs. 20%; RR 1.18; 95% CI 0.51 to 2.75). It was also not associated with any statistically significant differences in prescribing according to guidelines for rhinosinusitis (12% vs. 24%; RR 0.50; 95% CI 0.18 to 1.38), bronchitis (5% vs. 5%; RR 1.05; 95% CI 0.16 to 1.10), or exudative tonsillitis (53% vs. 44%; RR 1.19; 95% CI 0.51 to 2.81).

Table 13. Randomized controlled trials of augmenting interventions

Prescribing Pattern	Study and Characteristics	Design and Dates	Intervention and Control Details	Antibiotic Prescription Prescribing or Use
Overall Prescribing	Moore, 2009[108] Little, 2005[94] Patient N=807 Provider N=37 Age ≥3 y; acute cough illness, at least 1 symptom/sign localizing to the lower tract Fair quality	Balanced factorial RCT August 18, 1998 – July 30, 2003	Intervention: Delayed prescribing (prescription available on request if symptoms not resolved after 14 days) + Patient educational leaflet. Control: delayed prescribing only.	Intervention vs. Control Use of antibiotics 55% vs. 57%, (−2%) p=0.58
	MacFarlane, 2002[98] Patient N=259 Provider N=3 practices Adults; acute bronchitis Fair quality	Nested RCT September 1999 – August 2000	Intervention: Antibiotic prescription with advice to fill if symptoms worsened + information leaflet Control: Suggested delayed prescription alone	Intervention vs. Control % patients taking antibiotics after consultation: 47% vs. 62% (−15%), RR 0.76 (95% CI 0.59 to 0.97)
	Little, 2013[95] Europe Patient N=4,264 Practice N=246 Adults; acute URTI and LRTIs Fair quality	Cluster RCT October – December 2010 (baseline), February – May 2011 (intervention)	Intervention: Provider internet training on CRP testing and patient management + enhanced communication training. Control: CRP or communication training alone	Combined vs. Communication[a] Unadjusted RR 0.77 (95% CI 0.69 – 0.86) Combined vs. CRP Training Unadjusted RR 0.91 (95% CI 0.81 – 1.02)

Table 13. Randomized controlled trials of augmenting interventions (continued)

Prescribing Pattern	Study and Characteristics	Design and Dates	Intervention and Control Details	Antibiotic Prescription Prescribing or Use
Appropriate Prescribing	Samore, 2005[117] Patient N=407,460 Provider N=334 Children; acute RTIs Fair quality	Cluster RCT January – December 2001 (preintervention), January 2002 – September 2003 (postintervention)	Intervention: Community education to parents of children <6 y + electronic decision support. Control: community education alone.	Intervention vs. Control Change in prescribing for acute bronchitis and colds/ URTIs (deemed "never indicated") −32% vs. −5% (p=0.03) Overall Antibiotic Prescribing −9.7/100 person-years; p=0.03
	Briel, 2006[51] Patient N=552 Practice N=45 Provider N=30 Adults; acute RTI Fair quality	Cluster RCT January – May 2004	Intervention: 6-hour small-group seminar; 2-hour educational training in guidelines; 2-hour personal feedback by phone. Control: educational guideline training only.	Antibiotics prescribed per pharmacists: 13.5% vs. 15.7% adjusted OR 0.86 (95% CI 0.40, 1.93) Reported by clinicians: 15.1% vs. 16.7% adjusted OR 0.90 (95% CI 0.44, 1.98) Antibiotics prescribed according to guidelines: 53.8% vs. 53.1%; adjusted OR 1.03 (95% CI 0.30, 3.09

CI = confidence interval, CRP = C-reactive protein, LRTI = lower respiratory tract infection, N = sample size, OR = odds ratio, p = p-value, RR = relative risk, RTI = respiratory tract infection, URTI = upper respiratory tract infection, y = years

[a] Calculated by EPC.

Key Question 2. For patients with an acute respiratory tract infection, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?

Key Points

- Low-strength evidence based on one fair-quality trial (N=223) suggested that in children with AOM, delayed prescribing results in lower prevalence of resistance to 4 to 6 antibiotics compared with immediate prescribing.

Detailed Assessment

Delayed Prescribing

A fair-quality RCT of 223 children with nonsevere AOM comparing a form of delayed prescribing (in this study termed watchful waiting where parents needed to recontact the clinic if symptoms persisted) and immediate prescribing provided low-strength evidence that *S pneumonia* strains cultured from children in the immediate antibiotic group at day 12 were more likely to be multi-drug resistant (number of antibiotics: 0: 30% vs. 0%; 1−3: 42% vs. 44%; 4−6: 28% vs. 56%; $p<0.02$) while there were no difference at baseline.[102] The study also reported resistance to penicillin as significantly lower in the watchful waiting group (67% vs. 89%; $p<0.04$).

No other study reported on the impact of an intervention on antibiotic resistance rates relative to other interventions or to no intervention. One study of rapid strep testing reported on the specific resistance rates for isolates of S. pyogenes found in throat cultures of study participants but did not report these by intervention group.[101]

Key Question 3. For patients with an acute respiratory tract infection, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization, and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?

Key Points

Educational Interventions

- Low-strength evidence based on one fair-quality nonrandomized controlled trial and one fair-quality observational study suggested that educational interventions did not adversely affect medical complications as a result of decreased antibiotic prescribing for acute RTIs.

Clinical Interventions

Delayed Prescribing Strategies

- Delayed compared with immediate prescribing: There was low-strength evidence based on two good-quality trials that the only difference in adverse drug effects is a decrease in diarrhea in patients with AOM with use of delayed prescribing.

- Different strategies of delaying prescriptions: There was low-strength evidence based on one fair-quality trial of no differences in complications, diarrhea or rash, but giving prescriptions with instructions to delay had a higher rate of vomiting than with leaving prescriptions for collection and a higher rate of abdominal pain compared with requiring recontact.

C-Reactive Protein Point-of-Care Testing

- There was low-strength evidence based on seven fair-quality trials that hospitalization within 30 days was infrequent, and the use of CRP testing in the ED or primary care may increase risk of hospitalization within 1 month compared with usual care or a clinical algorithm, but the estimates are imprecise and there is some inconsistency in the findings.

Procalcitonin Point-of-Care Testing

- In adults, low-strength evidence based on one good-quality systematic review (four trials) suggested that use of a procalcitonin algorithm did not affect mortality or treatment failure at 30 days in primary care or ED patients with acute bronchitis, URTI, or presenting to primary care with upper or lower acute RTI.
- In children with suspected AOM, low-strength evidence based on one good-quality trial suggested that use of an adult procalcitonin algorithm does not affect a composite outcome measuring adverse events and lack of efficacy (OR 1.21; 95% CI 0.52 to 2.85) or hospitalizations (OR 1.41; 95% CI 0.68 to 2.93). Adverse effects associated with antibiotic use were more frequent with use of the algorithm than with procalcitonin (OR 3.03; 95% CI 1.11 to 9.22).

System-Level Interventions

- There was low-strength evidence based on one fair-quality trial of no difference in rates of pneumonia diagnoses or 30-day hospitalizations between electronic decision support compared with usual care or a paper-based support tool in patients with uncomplicated acute bronchitis.

Point-of-Care Tests Combined with Other Strategies

- There was low-strength evidence that the combination of training in enhanced provider communication plus use of CRP testing may increase risk of hospitalization compared with usual care, but not when compared with either intervention alone, regardless of the methods of training delivery.

Detailed Assessment

Educational Interventions

For the intervention strategy of education, two studies reported outcomes that are related to medical complications that may be associated with not using antibiotics in acute RTIs.[144,170,181] A large study of a public media campaign, aimed largely at parents of young children, found no statistically significant differences in diagnosis of several conditions identified as potential complications of acute RTIs, including pneumonia, peritonsillar abscess, retropharyngeal abscess, and epiglottitis using managed care organizations' administrative data from in the intervention and control cities before and after the intervention period.[144] An observational study

(N=819 children age 1−15 years) conducted in Norway in the late 1990's used both clinician and parent education aimed at reducing prescribing for AOM, using an evidence-based symposium and written guideline plus patient pamphlets and verbal information.[170] The study reported on the incidence of mastoiditis as a consequence of inappropriately withholding antibiotics for bacterial AOM but no cases were reported during the baseline or study periods. These studies provided low-strength evidence of no difference in the incidence of medical complications to draw conclusions about the potential impact of educational interventions on medical complications of acute RTI.

Communication Interventions

Strategies To Improve Communication Between Clinicians and Patients

Of the seven trials that studied interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs (Appendix D), only one fair-quality study assessed the outcome of hospitalization.[95] It found that slightly more patients treated by clinicians who received the communication intervention only were hospitalized within 4 weeks after the clinic visit (0.5%; 6/1,101) compared with the usual care group (0.2%; 2/861), but the difference was not statistically significant (RR 2.35; 95% CI 0.48 to 11.60).[95] When compared with patients in clinics using point-of-care CRP testing, fewer patients in the communication intervention group were hospitalized (0.5% [6/1,101] vs. 1.0% [10/1,018]; RR 0.56; 95% CI 0.20 to 1.52), which was also not statistically significant. Although there may be an increased risk with the communication intervention, the small size and relatively low quality of the single study prevents firm conclusions and this evidence is insufficient

Clinical Interventions

Delayed Prescribing Strategies

Delayed Compared With Immediate Prescribing

For adverse drug effects, the Cochrane review analyzed rates of diarrhea, rash, stomach ache, and vomiting, but did not pool results for any of these outcomes due to significant heterogeneity, which authors stated was likely due to the differences in types of antibiotics prescribed for each clinical condition.[22] For diarrhea, there was low-strength evidence that the only difference in antibiotic prescribing strategies is that, compared with immediate antibiotics, a delayed prescribing strategy significantly reduces diarrhea in children with AOM (8% vs. 21%; our pooled OR 0.35; 95% CI 0.21 to 0.59).[90,122] Otherwise, based on meta-analyses presented in the Cochrane review, there was no significant difference in diarrhea between delayed prescribing and immediate antibiotics in adults and children with cold (16% vs. 19%; OR 0.82; 95% CI 0.33 to 2.02)[44] or in adults and children with sore throat (13% vs. 11%; OR 1.23; 95% CI 0.67 to 2.28).[96] For the outcome of rash, there is low-strength evidence of no difference between delayed and immediate antibiotic prescriptions in children with AOM (5% vs. 4%; OR 1.21; 95% CI 0.41 to 3.58)[90] and in adults and children with sore throat (6.1% vs. 6.5%; OR 0.93; 95% CI 0.41 to 2.11).[96]

Different Strategies for Delaying Prescriptions

For patients with acute RTIs judged not to need immediate antibiotics, there was low-strength evidence that of no difference between different strategies of delaying prescriptions in

complications, but some differences in adverse drug effects. This evidence came from a fair-quality RCT of 433 patients seen across 25 primary care practices between March 2010 and March 2012 in the United Kingdom that compared giving prescriptions with instructions, leaving prescriptions for collection, postdating prescriptions, or requesting recontact, respectively.[92] Complication rates increased as the barriers to getting a prescription increased (0 percent for giving prescriptions with instructions, 1 percent for leaving prescriptions for collection, 0.9 percent for postdating prescriptions, and 3.7 percent for requesting recontact)but none reached statistical significance, although the difference between requesting recontact and leaving prescriptions for collection came closest (p=0.0619). For diarrhea, the largest difference was between giving prescriptions with instructions (21%) and requesting recontact (7%), but it did not reach statistical significance (p=0.0667). For rash, the largest difference was between giving prescriptions with instructions (9%) and leaving prescriptions for collection (2%) but it did not reach statistical significance (p=0.23). Vomiting rate was 18 percent in the group given prescriptions with instructions, which was statistically significantly greater than in the group left prescriptions for collection (4%; p=0.0447), but similar to the group given postdated prescriptions (18%) or in which recontact was requested (10%). Abdominal pain rate was 31 percent in the group given prescriptions with instructions, which was statistically significantly greater than in the group where recontact was requested (10%; p<0.0001), but similar to in the groups given postdated prescriptions (18%) and who were left prescriptions for collection (29%).

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

Five of the six studies included in the Cochrane review[27] reported that there had been no hospitalizations (published and unpublished data) within 28 days of initial consultation. The sixth study reported a small number of hospitalizations (30/4,121).[95] We included an additional fair-quality trial that also reported a small number of hospitalizations (6/128).[80] (Appendix D). With almost 9,000 patients involved and only 36 hospitalizations reported at followup, these studies indicate that hospitalization is infrequent, overall. We did not undertake pooling of these studies (the Cochrane review also did not pool) because of the differences in both patient populations (ED vs clinic-based) and intervention or comparators (i.e., one study used a clinical algorithm as the control).

One of the two trials reporting hospitalizations compared the effectiveness of a clinical algorithm with and without CRP testing as part of the algorithm in the ED.[80] The algorithm was used in an urban ED to guide chest x-ray and antibiotic treatment decisions for acute cough illness. The study found a non-statistically significant higher proportion of patients who were hospitalized within 30 days of the index visit when CRP testing was included as part of the algorithm compared with use of the clinical algorithm alone (6% [4/68] vs. 3% [2/60]; unadjusted RR 1.77; 95% CI 0.34 to 9.30; p=0.68). These higher frequencies may reflect a higher level of acuity among patients seen in the ED, and this small study may have been underpowered to identify a difference in hospitalizations.

The second trial found a higher proportion of patients treated by clinicians who received the CRP training were hospitalized within 4 weeks after the index clinic visit (1.0%; 22/2,159) compared with those in the group without CRP test training (0.4%; 8/1,962), a difference of borderline significance when adjusted for clustering for communication training received by some clinicians and other confounders (adjusted RR 2.91; 95% CI 0.96 to 8.85; p=0.06).[95] This

study was large and may have had adequate power to detect a difference, although a formal analysis of statistical power was not undertaken.

Together, these seven studies provide low strength evidence that the use of CRP testing in the ED or primary care may increase risk of hospitalization within 1 month compared with usual care or a clinical algorithm. It is low strength largely due to the inconsistency across studies, and the imprecision of the estimate, with few events, such that further studies could alter the findings.

Procalcitonin Point-of-Care Testing

In the systematic review (two publications) of procalcitonin algorithms used to help identify appropriate patients for antibiotic treatment in adults, mortality at 30 days was not affected in the primary care setting, where mortality rates were very low (0 of 507 algorithm patients and 1 of 501 control patients; OR 0.32; 95% CI 0.01 to 7.98).[23,24] This review also found that there were no differences between groups in mortality when stratified by diagnosis of URTI (0 of 282 vs. 1 of 267) or acute bronchitis (0 of 249 vs. 2 of 282). Evidence on mortality was low strength.

A composite measure of "treatment failure at 30 days" was also not different between groups in the primary care setting (OR 0.94; 95% CI 0.72 to 1.22). In this review, treatment failure in primary care was defined as death, hospitalization, acute RTI-specific complications (e.g., empyema for lower ARIs, meningitis for upper ARIs), recurrent or worsening infection, and still having acute RTI-associated discomfort at 30 days. Limiting this analysis to patients diagnosed with URTI did not alter the findings in a meaningful way (OR 0.95; 95% CI 0.73 to 1.24). This evidence was low-strength.

The single good-quality trial of using procalcitonin in children (ages 1 to 18 years) with LRTI provided low-strength evidence of a higher incidence of antibiotic adverse events in patients in the procalcitonin group the control group (26% vs. 10%, 16% absolute difference; OR 3.03; 95% CI 1.11 to 9.22).[45] This corresponds to the increased prescribing of antibiotics in the procalcitonin group. These adverse effects lasted a mean of 1.0 days in the procalcitonin group and 0.5 days in the control group, but this difference could have been affected by the repeat procalcitonin testing at days 3 and 5.

This study also evaluated the rate of hospitalization, and a statistically significant difference between the groups was not found (62% vs. 53%; OR 1.41; 95% CI 0.68 to 2.93). Duration of hospitalization was also not different (2.5 and 2.3 days [mean], respectively). The duration of hospitalization should also be considered in the light of repeated procalcitonin testing at days 3 and 5, which may have altered the course of continued antibiotic treatment. Using a composite measure, termed "safety", to measure both efficacy and adverse events (serious adverse events, disease-specific failure including hospitalization, recurrent infection requiring antibiotics, comorbidity requiring antibiotics, or worsening impairment of daily activity by ≥20%), low-strength evidence was unable to show a statistically significant difference between groups in patients with non-CAP LRTI diagnoses (OR 1.21; 95% CI 0.52 to 2.85).

System-Level Interventions

One system level study provided low-strength evidence of no difference in medical complications with electronic decision support compared with usual care or a paper-based support tool. In a trial of electronic decision support, there was no difference in the proportion of uncomplicated acute bronchitis patients who returned for a second physician visit within 30 days after their initial encounter and who were diagnosed with pneumonia. Similar proportions of patients, between 0.5 percent 1.5 percent, across the study groups returned for such care and were found to have pneumonia. There was no statistical difference between the groups.[81]

Hospital admissions within 30 days were rare, with between 0−0.1 percent patients returning across intervention or control sites.

Multifaceted Interventions

Point-of-Care Tests Combined With Other Strategies

There was low-strength evidence that the combination of training in enhanced provider communication plus use of CRP testing may increase risk of hospitalization compared with usual care. The IMPAC^{3}T trial and the GRACE consortium-supported trial (both described in Key Question 1 above) both reported rates of hospitalization for adults seen for upper[95] and LRTs by providers who were trained in CRP testing use, enhanced communication skills, or both, or who did not receive any training (usual care). The interventions differed in the method of training delivery, which was internet-based in the GRACE consortium trial[95] and conducted in small-groups on a face-to-face basis in the IMPAC^{3}T trial.[55] Based on our pooled analysis, the hospitalization rate was 1.1 percent in the combined intervention group, which was statistically higher than in the usual care group (0.2%; OR 4.65; 95% CI 1.21 to 17.87). Differences between the interventions groups were not found.

Key Question 4. For patients with an acute respiratory tract infection, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?

Key Points

Educational Interventions

- Low-strength evidence based on one good-quality trial and one fair-quality trial suggested that there is no difference in return visits for the index episode of acute RTI with educational interventions and moderate-strength evidence based on one good-quality trial and one fair-quality observational study suggested that patient education results in fewer overall clinic or ED visits for acute RTI in the year following the intervention compared with usual care.
  - The best evidence, a good-quality RCT found a 44 percent ($p<0.002$) reduction in "inappropriate" visits for URTIs and no difference in "necessary" visits based on clinical criteria. Results were similar across subgroups of age, race and insurance.
- Low-strength evidence based on one good-quality trial and one fair-quality trial suggested that patient or combined patient/clinician education interventions do not lead to differences in patient or parent satisfaction with clinic visits for acute RTI.

Communication Interventions

- There was low-strength evidence based on three fair-quality trials that the reduced prescriptions associated with communication interventions resulted in longer duration of symptoms, but better ratings of health at 2 weeks compared with usual care.

- In head-to-head comparisons, there was low-strength evidence based on three fair-quality trials that communication skills training and training and use of CRP testing resulted in similar rates of reconsultation and symptom resolution.

Clinical Interventions

Delayed Prescribing Strategies

- Delayed compared with immediate: Compared with immediate prescribing, although delayed prescribing was associated with reduced satisfaction (low-strength evidence based on two good-quality and three fair-quality trials included in one good-quality systematic review) and increased persistence of moderate to severe symptoms (low-strength evidence based on two fair-quality trials), it did not increase short-term or long-term reconsultation behavior. In fact, delayed prescribing may reduce return clinic visits in some cases, especially in patients with a history of receiving antibiotic prescriptions (low-strength evidence based on one good-quality observational study). We found no studies that compared ED visits or quality of life between delayed and immediate prescribing.
- Different strategies of delaying prescriptions: There was low-strength evidence based on one fair-quality trial that there are no differences in duration of moderately bad symptoms, reconsultations, or proportions of patients who were very satisfied with the consultation.
- Delayed prescribing versus clinical score: There was low-strength evidence based on one fair-quality trial that delayed prescribing leads an additional day of moderately bad or worse symptoms in patients with sore throat, but does not increase return visits before or after 1 month.

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

- Moderate-strength evidence from a pooled analysis of three fair-quality trials shows a greater risk of reconsultation within 4 weeks with a CRP testing intervention compared with usual care
- Low-strength evidence from four fair-quality trials that there is no difference in the effect of CRP testing on improvement of patients' symptoms or speed of improvement of symptoms compared with usual care.
- In head-to-head comparisons, low-strength evidence from two fair-quality trials found no effect of CRP testing on improvement of patients' symptoms compared with training in communication skills.
- In a head-to-head comparison, low-strength evidence from one large, fair-quality trial suggested no difference in the rate of reconsultation in a CRP group compared with a communication skills training group.

Procalcitonin Point-of-Care Testing

- Low-strength evidence based on one good-quality systematic review (three trials) suggested no differences between using and not using a procalcitonin algorithm in adults presenting to primary care with an URTI or LRTI in the number of days with limited

activity or missing work and patients with continuing symptoms at 28 days postbaseline. Evidence was insufficient to draw conclusions on quality of life, burden of illness.

Viral and S. Pneumococcal (Rapid Strep Tests) Point-of-Care Testing

- No studies.

System-Level Interventions

- There was low-strength evidence based on three fair-quality trials of no difference in ED visits and return outpatient clinic visits between electronic decision support and usual care.

Multifaceted Interventions

- There was low-strength evidence based on one fair-quality observational study of similar 1-month clinic attendance rates for patient education plus a physician-centered quality improvement project compared with usual care.
- Rapid streptococcal antigen detection test added to a decision rule: There was low-strength evidence based on one fair-quality trial that the combination of a rapid streptococcal antigen detection test plus a decision rule has comparable effects on symptom improvement and return visits compared with use of the clinical score alone or delayed prescribing.
- CRP plus provider-focused communication training: Compared with usual care, there was a longer duration of moderately bad symptoms, but comparable reconsultation rates, diagnostic testing use, and days off work. Compared with either intervention alone, there was low-strength evidence based on two fair-quality trials of comparable days of moderately bad symptoms, reconsultation rates, diagnostic testing use and days off work.

Detailed Assessment

Educational Interventions

Five studies of educational interventions reported on outcomes of additional healthcare utilization and patient satisfaction.[41,106,116,144,181] In the short term, two cluster RCTs found no difference in the rate of return visits following educational interventions, although statistical power for this outcome was not assessed in either study and the absolute differences are inconsistent across the studies. The good-quality study using an interactive booklet during clinic visits found no statistically significant difference in return visits within 2 weeks compared with usual care (12.9% vs. 16.2%, OR 0.75; 95% CI 0.41 to 1.38).[181] A fair-quality trial using a combination of clinician and adult patient education, including an ED waiting room computer kiosk, also found no difference between groups in return visits to the ED within 2 weeks, based on patient report. The proportion reporting they had returned increased from preintervention to postintervention more in the control group (5% vs. 1%; p=0.48).[106]

Additionally, two studies using patient or parent education examined new office or ED visits and found the impact of the interventions to be beneficial over longer time periods.[116,144] One large, fair-quality, observational study of a public media campaign found a reduction in subsequent visits (over 12 months) for children with a broad range of acute RTIs (p=0.01, point estimate for magnitude not reported).[144] Fairly large differences between the intervention and control cities in baseline office visits (net difference range 3 to 24 per 1,000 persons per month in

baseline year) were controlled for in the analysis (postintervention range of net differences were +10 to −15 per 1000 persons per month). The largest differences occurred near the end of the campaign period (late-winter/early spring) and then during the winter months. This study found no differences in adult visits for acute RTIs, but the intervention was loosely aimed at parents of young children. A good-quality RCT focused a pamphlet-based intervention only on reducing visits for URTI in adults or children and found significant reductions in visits (11 to 17 months after randomization) for URTI overall (−29%; $p<0.01$) as well as those deemed inappropriate (−44%; $p<0.002$).[116] The study team developed a list of criteria to differentiate URTIs that necessitate an office visit versus those that do not, for example any oral temperature above 103 degrees Fahrenheit. This study used careful methods to evaluate each case, and families who received/did not receive the intervention were followed up directly. No difference was seen in visits for necessary URTIs, or for AOM or other respiratory illnesses. Similar results were found across subgroups based on age, race and insurance.

Two cluster RCTs also reported patient satisfaction at 2 weeks of followup. The study of education patients/parents found no difference between groups in satisfaction with the visit (OR 0.64; 95% CI 0.33 to 1.22), feeling reassured after the visit (OR 0.84; 95% CI 0.57 to 1.25), or feeling enabled by what they had learned during their visit (OR 1.20; 95% CI 0.0.84 to 1.73).[76] The second study, using a combination of clinician and patient education, also found no difference in patient satisfaction 2 weeks post index visit, using a 5-point scale ($p=0.76$).[106]

Communication Interventions Versus Usual Care

Of the seven trials that studied interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs (Appendix D), five fair-quality studies reported on clinical outcomes other than use of antibiotics or medical complications (Table 14).[51,55-57,86,87,95] Relevant outcomes from a single trial were reported in three separate studies.[55-57] The studies assessed a variety of other clinical outcomes, including return clinic visits/reconsultation,[51,56,57,86,95] improvement in symptoms/speed of improvement,[51,55,87,95] patient satisfaction,[51,56] and quality of life.[86] All interventions targeted clinicians only, and used cluster randomization at the level of the clinic or the clinician. Two trials studied interventions specifically designed to improve shared decisionmaking, an approach in which the values, preferences and opinions of both the patient and the clinician are made explicit and considered in the decision.[86,87] Two trials[55-57,95] were factorial designs that assessed two interventions – one to enhance clinicians' communication skills and one to train clinicians in the use of point-of-care CRP testing. All but one intervention involved some form of in-person training by study personnel, while the fifth[95] included an internal practice-based meeting on prescribing issues. One intervention was mostly internet-based[95] and two others included some video or internet-based training.[86,87]

Return Clinic Visits or Reconsultation

Four trials reported on the outcome of return clinic visits or reconsultation.[51,56,57,86,95] These studies varied somewhat in their definitions of reconsultation, with one specifying "repeat consult for the same reason",[86] one specifying "reconsultation for new or worsening symptoms",[95] one specifying repeat visits for subsequent RTIs during more than 3 years of followup,[57] and two not specifying.[51,56] In a factorial design trial,[95] the reconsultation outcome was part of a composite outcome, "new or worsening symptoms" that included reconsultation for new or worsening symptoms, new signs, or hospital admission, as determined by medical record

review. Although reconsultations were not reported separately, 96 percent (730/760) of all patients with data on "new or worsening symptoms" had a reconsultation, with the remaining 4 percent having had hospital admissions. Two studies ascertained reconsultation at 2 weeks,[51,86] two studies at 4 weeks,[56,95] and one study at an overall mean of 3.67 years of followup.[57]

Evidence from three trials was insufficient to draw conclusions regarding the impact on communication interventions compared with usual care.[56,57,86,95] Pooling these data resulted in a high degree of heterogeneity, so is not presented ($I^{2=}$89%). Two trials found an increased reconsultation in groups receiving communication interventions. In the smaller of those trials the effect was not statistically significant (adjusted RR 1.3; 95% CI 0.7 to 2.3).[86] In the second and larger trial, the effect was borderline significant in a comparison of all patients who received the communication intervention versus those who did not, while adjusting for CRP testing (adjusted RR 1.33; 95% CI 0.99 to 1.74).[95] In the same study, the effect was significant in an unadjusted comparison of the communication only group with the usual care group (unadjusted RR 2.12; 95% CI 1.41 to 3.02).[95] This study – predominantly aimed at patients with LRTIs (80%), but including patients with URTI (20%) – found the increased relative risk of reconsultation among intervention group patients compared with usual care to be higher in those with URTI (adjusted RR 1.72; 95% CI 0.96 to 2.86) than in those with LRTI (adjusted RR 1.28; 95% CI 0.97 to 1.66), but with overlapping confidence intervals. The third trial found a decreased risk of reconsultation within 28 days (unadjusted RR 0.75; 95% CI 0.57 to 1.00; p=0.14, p-value from a model adjusted for CRP testing)[56] and a lower mean number of visits for subsequent RTIs per patient per year during a mean followup of 3.67 years (0.36 vs. 0.57; p=0.09).[57]

Improvement of Patients' Symptoms or Speed of Improvement of Symptoms

Four trials reported on the outcome of improvement of patients' symptoms or speed of improvement of symptoms.[51,55,87,95] These studies each assessed improvement of patient symptoms with a variety of different outcome measures, and found inconsistent effects overall. Three trials provided low-strength evidence that communication interventions resulted in longer duration of symptoms, but better ratings of health at 2 weeks compared with usual care.[55,87,95] In these studies, the various interventions were associated with: an increase in the proportion of patients who felt their health to be stable or improved at 2 weeks (mean difference 9%; p=0.08);[87] a statistically nonsignificant worse symptom severity score (mean difference 0.06, on a scale of 1−4; p=0.357);[95] prolonged time to resolution of symptoms rated as moderately bad or worse (median days: 6 vs. 5; adjusted HR 0.79; 95% CI 0.67 to 0.92);[95] and no difference in mean number of days off of work (3.37 [SD 4.02] vs. 3.37 [SD 3.77]).[55]

As with other outcomes, a factorial design trial reported on differences according to lower LRTI versus URTI. They found no difference in mean symptom severity score between the communication and usual care groups in patients with LRTIs (1.83 vs. 1.84; p=0.775); but did find a worse mean score for the communication group in patients with URTI (1.69 vs. 1.44; p=0.044).[95] While moderately bad symptoms were slower to resolve among the communication group compared with the usual care group overall, this difference was more pronounced in patients with URTI than in those with LRTI. In the subgroup with LRTI, the difference in median days to resolution between communication group and usual care was the same as in the overall group (6 vs. 5; adjusted HR 0.83; 95% CI 0.70 to 0.99) while in those with URTI the difference was greater (5 vs. 3.5; adjusted HR 0.66; 95% CI 0.48 to 0.89).

Patient Satisfaction

One trial reported on patient satisfaction with a communication intervention compared with usual care.[56] The study (N=431) reported on the proportion of patients who were at least "very satisfied" and found no difference between the communication intervention and usual care (79% vs. 74%; unadjusted RR 1.06; 95% CI 0.95 to 1.18).

Quality of Life

Quality of life was reported in a single study (N=359), providing insufficient information to assess the strength of evidence.[86] The investigators used the SF-12 survey to assess patients' physical and mental quality of life. They found no statistically significant difference between the communication and usual care groups in scores for either the physical or mental scale. The communication group had a slightly higher mean score on the physical scale (49.4 vs. 48.2) and a slightly lower mean score on the mental scale (50.8 vs. 51.2).

Use of Other Diagnostic Tests

Only one trial (N=431) reported the effect of a communication skills training intervention on the use of other diagnostic testing compared with either usual care, resulting in insufficient strength of evidence to draw conclusions.[55] The study reported on a small number of events and found no significant differences between the CRP group and usual care in the use of: chest x-ray (5% vs. 7%), blood testing (1% vs. 0%), or other tests such as spirometry or sputum analysis (0% vs. 2%).

Communications Interventions Versus C-Reactive Protein Testing (Head-to-Head Comparisons)

Return Clinic Visits or Reconsultation

Low-strength evidence from one large fair-quality factorial design trial (N=2,119) indicated no difference in reconsultation in a communication skills training group compared with a group trained in CRP testing (20.3% vs. 23.5%; unadjusted RR 0.86; 95% CI 0.74 to 1.01) (Table 14).[95] This trial also reported on differences according to lower LRTI versus URTI.[95] Evidence from one trial (N=552) provided insufficient information to assess the strength of evidence regarding a communication intervention in conjunction with prescribing guideline education compared with the education component alone (Table 14).[51] This study found no association of the communication intervention with reconsultation within 14 days (adjusted RR 0.97; 95% CI 0.78 to 1.21).

Improvement of Patients' Symptoms or Speed of Improvement of Symptoms

Low-strength evidence from two trials found no effect of training in communication skills on improvement of patients' symptoms compared with CRP testing (Table 14).[55,95] These studies each used a different intervention and assessed improvement of patient symptoms or speed of improvement of symptoms with various outcome measures. They found no significant differences between CRP testing and communication training in the outcomes of: mean days off of work (3.37 vs. 3.35);[55] symptom severity score (1.81 [SD 1.02] vs. 1.70 [SD 1.00]);[95] or median number of days to resolution of symptoms (6 [IQR 3:10] vs. 5 [IQR 3:8]).[95]

Evidence from one trial (N=552) provided insufficient information to assess the strength of evidence regarding a communication intervention in conjunction with prescribing guideline

education compared with the education component alone (Table 14).[51] This study found a statistically nonsignificant reduction in the mean number of days with restricted activity (6.18 vs. 6.81; adjusted mean difference 0.40; 95 % CI 1.07 to 0.27), and no difference in the proportion of patients being off of work within 14 days (OR 1.00; 95% CI 0.63 to 1.57).[51]

Patient Satisfaction

Patient satisfaction was reported in a study (N=552) that compared a communication intervention in conjunction with prescribing guideline education versus the education component alone.[51] The study assessed the proportions of patients with a maximum score of 70 (scale 14 to 70) on a patient satisfaction measure, using that outcome because the scores were highly skewed. They found no difference between the communication/education and education only groups in the proportion of patients with a maximum satisfaction score (47.8% vs. 49.0%; adjusted OR 1.00; 95% CI 0.64 to 1.31).[51]

Use of Other Diagnostic Tests

Only one trial (N=431) reported the effect of a communication skills training intervention on the use of other diagnostic testing compared with CRP testing, resulting in insufficient strength of evidence to draw conclusions.[55] The study reported on a small number of events and found no significant differences between the CRP group and communication skills training for the same outcomes: chest x-ray (5% vs. 5%), blood testing (1% vs. 1%), and other tests (0% vs. 2%).

Table 14. Interventions to improve communication between clinicians and patients

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Briel, 2006[51] Practice N=30 Provider N=30 Patient N=552 Patients ≥ 18 y; acute RTI Fair quality	Cluster RCT (clinic level). January 2004 – May 2004 Followup: 14 days	Intervention: *Communication + Education*: 6-hour small-group seminar in patient-centered communication; 2-hour educational training in guidelines adapted by investigators; 2-hour personal feedback by phone after intervention. *Education only*: Educational intervention on guidelines, only (2-hour training). Control: no intervention (nonrandomized).	Communication + Education vs. Education only: Reconsultation within 14 days: 44.7% vs. 49.3%; adjusted RR (95% CI): 0.97 (0.78 to 1.21). Days with restricted activities (mean): 6.18 vs. 6.81; adjusted difference: −0.40 (95% CI −1.07 to 0.27). Patients off work within 14 days: 53.4% vs. 47.2%; adjusted OR (95% CI): 1.00 (0.63 to 1.57). Patients with satisfaction score of 70 out of 70 (%): 47.8% vs. 49.0%; adjusted OR (95% CI): 1.00 (0.64 to 1.31).
Cals, 2009[56] Practice N=20 Provider N=40 Patient N=431 Adults; suspected LRTI and cough <4 weeks Fair quality	2 X 2 factorial cluster RCT (clinic level). September 2005 - March 2006 and September 2006 - March 2007. Followup: 28 days for most patients (maximum 10 weeks).	Intervention: *Communication skills training*: based on 11 key tasks (e.g., exploring patient's fears and expectations, asking patient's opinion of antibiotics), and elicit-provide-elicit framework. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual Care	Communication + Combination vs. CRP + Control: Reconsultation within 28 days: 27.8% vs. 37.0%; unadjusted RR 0.75, 95% CI 0.57 to 1.00; p=0.14 (p-value from model adjusted for practice level). Patient satisfaction (% at least very satisfied): 78.7% vs. 74.4%; unadjusted RR 1.06, 95% CI 0.95 to 1.18; p=0.88 (p-value from model adjusted for practice level).

Table 14. Interventions to improve communication between clinicians and patients (continued)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Cals, 2011[55] (see Cals, 2009[56])	See Cals, 2009[56]	See Cals, 2009[56] (above)	Days off of work, days (SD): Communication vs. Control: 3.37 (4.02) vs. 3.37 (3.77) Communication vs. CRP: 3.37 (4.02) vs. 3.35 (4.54) Use of other diagnostic testing: Chest X-ray: Communication vs. Control: 5% vs. 7% Communication vs. CRP: 5% vs. 5% Blood tests: Communication vs. Control: 1% vs. 0% Communication vs. CRP: 1% vs. 1% Other (spirometry, sputum): Communication vs. Control: 0% vs. 2% Communication vs. CRP: 0% vs. 2%
Cals, 2013[57] (see Cals, 2009[56]) Patient N=379	See Cals, 2009[56]	See Cals, 2009[56] (above)	Office visits for RTIs during followup (mean overall followup of 3.67 years), Mean No. per patient per year (95% CI): Communication + Combination vs. CRP + Control: 0.36 (0.30 to 0.42) vs. 0.57 (0.46 to 0.69), p=0.09 (p-value from model adjusted for practice level).
Légaré, 2010[87] Practice N=4 Provider N=33 Patient N=459 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2007 – March 2008 Followup: 2 weeks	Intervention: Interactive workshops on URTIs, risk communication, fostering patient participation in decisionmaking, shared decisionmaking support tools. Control: Delayed intervention.	Patients who felt they had “stable”, “a little better”, or “much better” health at 2 weeks (compared with “not much worse” or “much worse”): Baseline: 87% vs. 91% After experimental group received intervention (Time 1): 94% vs. 85% After control group received intervention (Time 2): 94% vs. 91% Difference at Time 1 (95% CI): 9 (−2 to 18), p=0.08.
Légaré, 2012[86] Practice N=9 Provider N=149 Patient N=359 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2010 – April 2011 Followup: 2 weeks	Intervention: 2-hour online tutorial and 2-hour onsite interactive workshop on decisionmaking about antibiotic treatment for RTIs and communication with patients. Control: Usual care.	Reconsultation for same reason: Baseline: 21.6% vs. 13.4% After intervention: 22.7% vs. 15.2% Adjusted RR (95% CI): 1.3 (0.7−2.3). Patient QOL (physical scale, 0−100): Baseline: 49.3 vs. 47.7 After intervention: 49.4 vs. 48.2 Mean difference: 0.4 (95% CI −2.6 - 3.3). Patient QOL (mental scale, 0−100): Baseline: 51.2 vs. 48.5 After intervention: 50.8 vs. 51.2 Mean difference: −1.9 (95% CI −4.9 - 1.1).

Table 14. Interventions to improve communication between clinicians and patients (continued)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Little, 2013[95] Practice N=228 Provider N=372 Patient N=4,121 Patients >18 y; acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster RCT (clinic level). February 2011 – May 2011. Followup: 4 weeks	Interventions: *Communication skills training*: Internet-based training in communication skills; interactive booklet; video demonstrations. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual care.	Reconsultation for new or worsening symptoms within 4 weeks (composite outcome including hospital admissions, of which 3.9% (30/760) overall was hospital admission): Communication + Combination vs. CRP + Control: 20.1% vs. 16.4%; adjusted RR (95% CI): 1.33 (0.99 to 1.74). Communication vs. Control: 23.5% vs. 11.8%; adjusted RR (95% CI): 2.12 (1.41 to 3.02). Communication vs. CRP: 20.3% vs. 23.5%; unadjusted RR (95% CI): 0.86 (0.74 to 1.01). Symptom severity score (1−4) 2 to 4 days after consultation: Communication + Combination vs. CRP + Control: 1.84 vs. 1.73; adjusted mean difference: 0.07 (95% CI -0.03 to 0.16). Communication vs. Control: 1.81 vs. 1.75; adjusted mean difference: 0.06 (95% CI - 0.07 to 0.20). Communication vs. CRP, mean (SD): 1.81 (1.02) vs. 1.70 (1.00) Resolution of symptoms rated "moderately bad" or worse (median days): Communication + Combination vs. CRP + Control: 6 vs. 5; adjusted HR: 0.83 (95% CI 0.74 to 0.93). Communication vs. Control: 6 vs. 5; adjusted HR: 0.79 (95% CI 0.67 to 0.92). Communication vs. CRP, median (IQR): 6 (3:10) vs. 5 (3:8)

CI = confidence interval, CRP = C-reactive protein, HR = hazard ratio, IQR = inter-quartile range, LRTI = lower respiratory tract infection, N = sample size, OR = odds ratio, p = p-value, QOL = quality of life, RCT = randomized controlled trial, RR = relative risk, RTI = respiratory tract infection, SD = standard deviation, URTI = upper respiratory tract infection, y = years

Clinical Interventions

Delayed Prescribing Strategies

Delayed Versus Immediate Prescribing (Usual Care)

Clinic Visits

Four fair-quality RCTs provided moderate-strength evidence that risk of reconsultation within a month was similar for delayed and immediate prescription strategies in adults and children with cough[70,94] and children with sore throat[110] or AOM[122] (Table 15). However, there was low-strength evidence that a delayed prescribing approach may reduce risk of reconsultation within a month in adults with sore throat based on findings from a good-quality prospective cohort study that compared three antibiotic prescribing strategies (immediate, delayed, or no) in 12,829 adults presenting to primary care.[153] Although there is no formal direct statistical comparison between delayed and immediate prescribing strategies, since the magnitude of the

reduction in risk of reconsultation is larger for delayed prescribing and the overlap of confidence intervals in minimal, it is possible that delayed prescribing statistically significantly reduces risk of reconsultation compared with immediate prescribing specifically in patients with sore throat. There was low-strength evidence that at 5 to 6 months after the index visit, reconsultation rates are similar for delayed and immediate prescribing for cough and children with sore throat.[70,78]

Table 15. Reconsultations for delayed compared with immediate antibiotic prescribing

Study Design Population and Setting Sample Size	Results
Dowell, 2001[70] RCT Uncomplicated RTI in primary care N=191	% patients with ≥ 1 reconsultations for similar complaints: Within 1m: 12% vs. 12%; p=0.93 Within total followup (minimum 6 month): 39% vs. 40%; p=0.85
Little, 2005[94,108] RCT Uncomplicated RTI in primary care N=402	Mean attendances within 1 month: Delayed=0.12 vs. Immediate=0.11; p=NR
Little, 2014[153] Prospective cohort Acute sore throat in primary care N=11,950	RR (95% CI) of reconsultation within a month, range across models: Immediate vs. no: 0.76 (0.66 to 0.87) to 0.83 (0.73 to 0.94) Delayed vs. no: 0.57 (0.47 to 0.68) to 0.61 (0.50 to 0.74)
Gerber, 1990[78] RCT Children with streptococcal pharyngitis in a private pediatric office N=113	Unscheduled visits at 5 months: 53% vs. 44%; p=0.18
Pichichero, 1987[110] RCT Children with Group A beta-hemolytic streptococcal pharyngitis in a private pediatric practice N=114	Reconsultation: 14% vs. 17%, p=0.73[a]
Spiro, 2006[122] RCT Children with AOM in the ED N=283	Unscheduled visits: 4−6 days: 10% vs. 8%, p=0.70 11−14 days: 15% vs. 11%; p=0.51

AOM = acute otitis media, CI = confidence interval, ED = emergency department, N = sample size, NR = not reported, p = p-value, RCT = randomized controlled trial, RTI = respiratory tract infection

[a] Reconsultation rates from Cochrane Review[22] but could not find in primary study publication and time period unknown. EPC calculated p-value.

Symptoms

Eight RCTs used diverse methods to compare symptomatic improvement between delayed and immediate prescribing strategies (Table 16).[44,70,72,90,94,96,110,122] Among all the findings, however, the most clinically meaningful evidence on patient symptoms comes from two RCTs that assessed duration and rate of moderately bad to severe symptoms that were clearly noticeable to a patient.[72,94] Together, findings from these studies provided low-strength evidence that, compared with immediate antibiotics, a delayed antibiotic strategy increases risk of severe sore throat related symptoms persisting at day 3 and may increase duration of *moderately bad* cough-related symptoms by approximately 1 day.[94] We did not pool data from these two RCTs due to the diversity in clinical presentation (i.e., adults and children with cough as main symptom[94] compared with children with pharyngitis[72]) and outcome assessment (i.e., duration of moderately bad symptoms[94] compared with proportion of patients with severe symptoms[72]). In

the RCT of 229 children with pharyngitis seen at pediatric clinics at a University hospital in Jordan between 1988 and 1989, at day 3, delayed prescribing was associated with a higher risk ($p<0.0001$) of sore throat (52% vs. 1%), difficult swallowing (40% vs. 0%), decreased activity (50% vs. 13%), decreased appetite (42% vs. 4%), headache (7% vs. 0%), cervical lymphadenopathy (40% vs. 1%), irritability (4% vs. 0%), abdominal pain (16% vs. 0%), and vomiting (17% vs. 0%).[72] The RCT that measured duration of moderately bad symptoms used a factorial design to randomize 807 primarily adult patients who presented to primary care clinics in South West England between 1998 to 2003 to no antibiotics, immediate antibiotics, or delayed antibiotics, with or without an information leaflet.[94] Here we only focused on the groups that did not receive the information leaflet. Although this RCT did not directly compare the delayed and immediate prescribing strategies, indirect evidence from their respective comparisons to no antibiotics suggest a longer duration of moderately bad symptoms with delayed antibiotics. Compared with no antibiotics, duration of moderately bad symptoms with delayed antibiotics was similar (mean difference, 0.14; 95% CI −0.87 to 1.14), but was reduced by 1.08 days with immediate antibiotics (95% CI −2.1 to −0.09). However, it is unclear what value a 1-day difference in moderately bad symptoms is to patients.

Otherwise, compared with an immediate antibiotic prescribing approach, fever was the only symptom that was consistently statistically significantly worsened by delayed antibiotic prescribing (Table 16).[44,72,96,110,122] However, the clinical importance of the findings were unclear because the differences were marginal in size and of questionable value to the patients (i.e., a day or less in duration, only up to 0.6 degrees Fahrenheit) and they were not accompanied by significant effects on the resolution of various other symptoms.

Table 16. Fever and symptom duration for delayed versus immediate antibiotic prescribing

Study Population Sample Size	Fever	Speed of Any Symptom Improvement
Spiro, 2006[122] AOM N=238	Total days of fever: 2.3 vs. 1.7; p=0.03	Total days of otalgia: 3.0 vs. 2.7; p=0.35
Little, 2001[90] AOM N=315	NR	Duration of symptoms in days (all *P*<0.01): Earache: 3.57 vs. 2.56; ear discharge: 1.21 vs. 0.56; night disturbance: 2.35 vs. 1.64; crying: 2.23 vs. 1.54
Arroll, 2002[44] Common cold N=129	Temperature Fº at Day 10: 96.98 vs. 97.34; p=0.039	NR
Dowell, 2001[70] Cough N=191	NR	Cough continuing at 13 days: 32% vs. 30% “No difference in duration of other recorded symptoms.” (data NR)
Little, 2005[94] Cough N=269	NR	Duration of symptoms not different between delayed or immediate antibiotics.
Little, 1997[96] Sore throat N=481	Total days of fever: 2 vs. 1; p=0.04	Median duration in days (all p≥0.39): Sore throat=5 vs. 4; cough=3 vs. 3; headache=2 vs. 2; unwell=3 vs. 4

Table 16. Fever and symptom duration for delayed versus immediate antibiotic prescribing (continued)

Study Population Sample Size	Fever	Speed of Any Symptom Improvement
El-Daher, 1991[72] Sore throat N=229	Change in temperature, Fº, from Day 1 to 3 (estimated from Figure 2): 101.7 to 100.4 vs. 101.8 to 100.0; p=0.0001	NR
Pichichero, 1987[110] Sore throat N=114	Change in temperature, Fº, from Day 1 to 3 (estimated from Figure 2): 100.8 to 98.9 vs. 100.5 vs. 98.3; p=0.022	NR

N = sample size, NR = not reported, p = p-value.

Patient Satisfaction

We relied on findings from a good-quality Cochrane review meta-analysis for evaluating the comparative satisfaction of delayed versus immediate antibiotics.[22] Results from five RCTs of 1334 adults and children with cold,[44] cough,[70,94] sore throat,[96] or children with AOM[90] provided moderate-strength evidence that up to 2 weeks after their visit, significantly fewer patients are satisfied or very satisfied with delayed antibiotics (85% vs. 95%; OR 0.52; 95% CI 0.35 to 0.76).

Return to Work or School

Compared with immediate antibiotics, delaying antibiotics did not statistically significantly increase days missed from work or school in adults with sore throat (median, 1 compared with 2; p=0.13)[96] or in children with AOM (mean, 2.15 compared with 1.97; p=0.56).[90]

Other Treatments

Compared with immediate antibiotics, delaying antibiotics did not statistically significantly increase days of analgesic use in adults with sore throat (4 compared with 3; p=0.46).[96] In children with AOM, delaying antibiotics statistically significantly increased daily number of spoons of paracetamol in the first 3 days after presenting in primary care (2.28 compared with 1.69; p<0.01),[90] but did not increase total days of otic analgesia use (3.2 compared with 3.7; p=0.22) or total days of ibuprofen or acetaminophen (3.2 compared with 2.9; p=0.26) in the 11 to 14 days following ED presentation.[122]

Different Strategies of Delaying Prescriptions

For patients with acute RTIs judged not to need immediate antibiotics, there was low-strength evidence that there are no statistically significant differences between different strategies of delaying prescriptions in duration of moderately bad symptoms, reconsultations, or proportions of patients who were very satisfied with the consultation. This evidence came from a fair-quality RCT of 433 patients seen across 25 primary care practices between March 2010 and March 2012 in the United Kingdom.[92] Giving prescriptions with instructions, leaving prescriptions for collection, postdating prescriptions, or requesting recontact, respectively, led to similar median days of symptoms rated as moderately bad (4 for all), proportions of patients with reconsultations within 1 month (14%, 14%, 10%, 18%; p=0.563) or after 1 month (37%, 32%, 39%, 39%, p=0.391) and proportions of patients who were very satisfied with the consultations (89%, 89%, 80%, 74%, p=0.667). Satisfaction results were available for only 24 percent of the patients.

Outcomes by Subgroups

Some evidence was available to assess variation in reconsultation and satisfaction outcomes based on some subgroup characteristics of interest.

Diagnosis

Type of RTI or setting did not clearly influence the impact of delayed prescribing on reconsultation within the month following the index visit since there was very little variation in the rate difference compared with immediate prescribing for children with AOM seen in the ED (+4%, 11−14 days: 15% vs. 11%; p=0.51),[122] adults and children with uncomplicated RTO seen in primary care in England (0% to +1%, 12% vs. 11% to 12%),[70,94] or children from middle and upper class families with Group A beta-hemolytic streptococcal pharyngitis seen at a private pediatric practice located in suburban Rochester, New York (−3%; 14% vs. 17%, p=0.73).[110]

Clinician Characteristics

For satisfaction, results of the Cochrane review's statistical heterogeneity testing suggested against any clear differences according to variation in patient or clinician characteristics, diagnostic method, or contextual factors for the comparison of delayed versus immediate antibiotics (Chi^2=4.28, df=4, p=0.37; I^2=6%) of delayed versus no antibiotics (Chi^2=0.42, df=2, p=0.81; I^2=0%).[22]

Age

We observed that the strongest effect estimates of satisfaction came from studies of children with AOM compared with studies of adults and children with sore throat, cough, or cold both for the comparison of delayed versus immediate antibiotics and the comparison of delayed versus no antibiotic. Compared with immediate antibiotics, rates of participants who were satisfied or very satisfied were lowest with delayed prescribing in the study of children with AOM (77% vs. 91%, OR 0.32; 95% CI 0.16 to 0.65).[90] The difference was increasingly smaller in adults and children with cough (82% vs. 90%, EPC pooled OR 0.55; 95% CI 0.33 to 0.92),[70,94] sore throat (93% vs. 96%; OR 0.61; 95% CI 0.25 to 1.49),[96] and cold (95% vs. 94%; OR 1.47; 95% CI 0.32 to 6.85).[44] Likewise, compared with no antibiotics, the strongest increase in satisfaction with delayed antibiotics was in a trial of children with AOM (95% vs. 91%; OR 2.00; 95% CI 0.65 to 6.18)[60] and was increasingly smaller in trials of adults and children with sore throat (93% vs. 90%; OR 1.49; 95% CI 0.70 to 3.19)[96] or cough (77% vs. 72%; OR 1.34; 95% CI 0.84 to 3.19).[94] However, for the comparison of delayed versus no antibiotics, the difference in type of setting between the study of children with AOM and those in adults and children with sore throat or cough (ED versus general practice) may have contributed to the somewhat stronger increase in satisfaction with delayed antibiotics as well.

Delayed Prescribing Versus Clinical Score (Head-to-Head Comparison)

There was low-strength evidence that delayed prescribing leads to an additional day of moderately bad or worse symptoms in patients with sore throat, but does not increase return visits before or after 1 month. This evidence came from a fair-quality RCT of 48 general practitioners and triage practice nurses in general practices in south and central England who saw people ages ≥3 presenting with acute sore throat (2 weeks or less of sore throat) and an abnormal looking throat (e.g. erythema and/or pus) between October 2008 and April 2011.[91] The clinical score used was FeverPAIN, which involved offering immediate antibiotics for score ≥4, delayed antibiotics for scores of 2−3, and no antibiotics for scores of 0−1. The delayed prescription

strategy was to leave the prescription for collection after 3−5 days. Duration in days of symptoms rated as moderately bad or worse was 5 for delayed prescribing and 4 for clinical score (HR 1.30; 95% CI 1.03 to 1.63). There were no differences between the clinical score group and the delayed prescribing group in proportion of patients with return visits within 1 month (8% vs. 8%; RR 0.91; 95% CI 0.47 to 1.72) or after 1 month (12% vs. 15%; RR 0.79; 95% CI 0.47 to 1.29).

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing Versus Usual Care

We relied on findings from a good-quality Cochrane review,[27] in addition to findings from our search and review, for evaluating CRP testing compared with usual care for clinical outcomes other than use of antibiotics or medical complications. The Cochrane review included six RCTs that reported on various clinical outcomes (Table 17).[56,58,68,95,179,180] In addition, we included one fair-quality study that compared the effectiveness of a clinical algorithm with and without point-of-care CRP testing as part of the algorithm in an urban emergency department.[80] This study was excluded from the Cochrane review on the basis of not being in a primary care setting;[27] however, EDs were included in our protocol. The trials assessed a variety of clinical outcomes, including return clinic visits/reconsultations,[56-58,80,95] improvement in symptoms/speed of improvement,[55,58,68,95,179,180] patient satisfaction,[56,58] and use of other diagnostic testing.[55,179] All interventions targeted clinicians only. Four trials were randomized at the level of the patient[58,68,80,180] and three were cluster randomized at the level of the clinic or the clinician.[55-57,95,179] Two trials[55-57,95] were factorial designs that assessed two interventions – one to enhance clinicians' communication skills and one to train clinicians in the use of CRP testing.

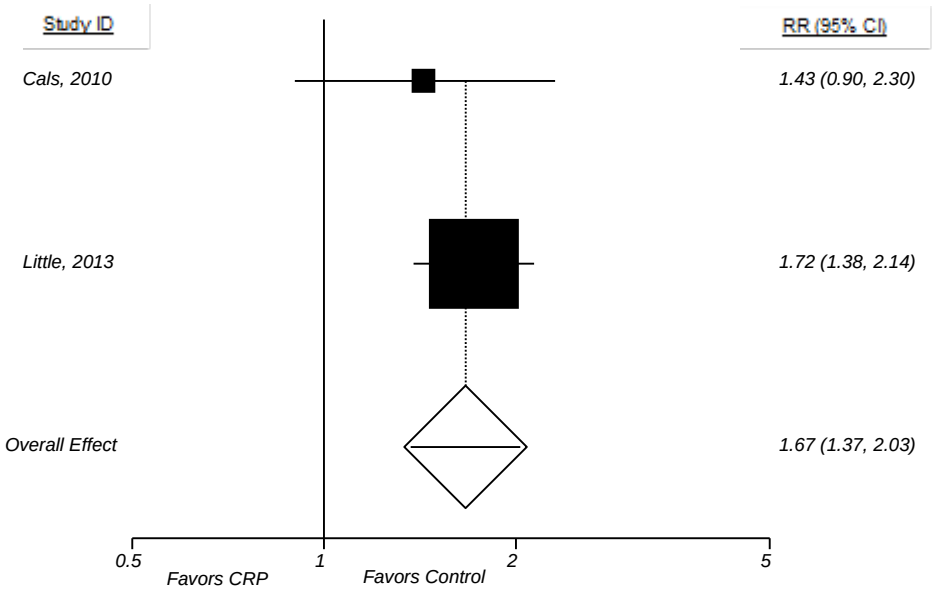
Return Clinic Visits or Reconsultation

Four published trials reported on the outcome of return clinic visits or reconsultation.[56-58,80,95] These studies varied somewhat in their definitions of reconsultation, with one specifying "reconsultation for new or worsening symptoms",[95] one specifying repeat visits for subsequent RTIs during more than 3 years of followup,[57] one specifying subsequent office or ED visits,[80] and two not specifying.[56,58] In a factorial design trial,[95] the reconsultation outcome was part of a composite outcome, "new or worsening symptoms" that included reconsultation for new or worsening symptoms, new signs, or hospital admission, as determined by medical record review. Although reconsultations were not reported separately, 96 percent (730/760) of all patients with "new or worsening symptoms" had a reconsultation, with the remaining 4 percent having had hospital admissions. All four studies ascertained reconsultation at 4 weeks[56,58,80,95] and one study also reported on return clinic visits for RTIs at an overall mean of 3.67 years of followup.[57]

The Cochrane review conducted a pooled analysis of the proportions of patients with reconsultations within 28 days of the index visit. They included three studies (Cals, 2009; Cals, 2010; and Little, 2013), but excluded one study (Gonzales, 2011) based on its emergency department setting. In addition, they included unpublished data from another study.[179] As in their pooled analysis of antibiotic prescribing, the Cochrane review included patients in two studies[56,95] whose physicians had received an intervention to improve communication around antibiotic prescribing. They found a small statistically non-significant increase in the risk of consultation in the CRP groups compared with the non-CRP groups, with a pooled relative risk of 1.08 (95% CI 0.93 to 1.27; I^2=34%). To better characterize the specific effect of CRP testing alone compared with usual care (i.e., no intervention), we conducted a pooled analysis of the two

studies that published data on groups receiving CRP testing only compared with groups receiving usual care.[58,95] The relative risk for reconsultation within 28 days was higher in the CRP group (RR 1.67 95% CI 1.37 to 2.03; I^2=non-estimable) (Figure 4); a greater difference than in the Cochrane review, which is consistent with the idea that including the communication intervention in the analyses muted the observed effect of CRP testing alone. In a sensitivity analysis that included the unpublished data reported in the Cochrane review,[179] the pooled relative risk was slightly lower, but still statistically significant (RR 1.64; 95% CI 1.35 to 2.00; I^2=0%). These findings provide moderate-strength evidence that CRP testing increases the risk of reconsultation compared with usual care.

Figure 4. Reconsultation within 28 days: C-reactive protein testing compared with usual care



CI = confidence interval, CRP = C-reactive protein, RR = relative risk

In a trial predominantly aimed at patients with LRTIs (80%), but including patients with URTI (20%), differences in the relative risk of reconsultation according to LRTI versus URTI[95] between those in the CRP group compared with usual care were not found; URTI adjusted RR 2.03 (95% CI 0.78 to 4.47) or in those with LRTI adjusted RR 1.67 (95% CI 1.09 to 2.48), with overlapping confidence intervals.

CRP Testing Compared With Other Strategies (Head-to-Head Comparisons)

There was insufficient evidence regarding the effectiveness of CRP testing as part of a clinical algorithm compared with the algorithm alone.[80] A single trial (N=131) found a nonsignificantly higher proportion of return visits in the CRP group: 40 percent (95% CI 28 to 52) vs. 33 percent (95% CI 21 to 45), p=0.46. As noted above, low-strength evidence from one large fair-quality trial (n=2119) indicated no significant difference in the rate of reconsultation in a CRP group compared with a communication-training group (23.5% vs. 20.3%; unadjusted RR 1.16; 95% CI 0.99 to 1.40).[95]

Improvement of Patient Symptoms or Speed of Improvement of Symptoms

There was low-strength evidence from four trials of no significant differences between CRP testing and usual care regarding the effect of CRP testing on improvement of patients' symptoms compared with usual care.[55,58,68,95] These studies each used different interventions and assessed improvement of patient symptoms or speed of improvement of symptoms with a variety of outcome measures. They found no significant difference in: proportion of patients feeling recovered on day 7 (23% vs. 25%, p=0.73),[58] "substantially improved" by day 7 (45% vs. 41%, p=0.57) or by day 28 (72.4% vs. 67.8%, p=0.45),[180] mean days off of work (3.35 vs. 3.37),[55] a symptom severity score with a range of 1 to 4 (1.79 vs. 1.79),[95] or median number of days to resolution of symptoms (5 vs. 5; adjusted HR 0.87; 95% CI 0.74 to 1.03).[95] One study found a higher proportion of patients in the CRP group with "increased or unchanged morbidity" but did not define morbidity (12% vs. 8%; OR 1.6; 95% CI 1.0 to 2.6).[68]

As with other outcomes, the factorial design trial[95] reported on differences according to LRTI versus URTI. They found a nonsignificantly lower mean symptom severity score for the CRP group compared with usual care in patients with LRTIs (1.72 vs. 1.84; p=0.707) and a nonsignificantly worse mean score for the CRP group in patients with URTI (1.63 vs. 1.44; p=0.186).[95] While no difference was found in the time to resolution of moderately bad symptoms among the CRP group compared with the usual care group overall, a small nonsignificant increase in time to resolution was found in patients with URTI (4 vs. 3.5; adjusted HR 0.81; 95% CI 0.59 to 1.11). In the subgroup with LRTI, the difference in median days to resolution between CRP group and usual care was the same as in the overall group (5 vs. 5; adjusted HR 0.89; 95% CI 0.77 to 1.07). Another trial reported on the proportion of patients feeling recovered on day 7 according to type of RTI: LRTI and rhinosinusitis.[58] The study found that among patients with LRTIs a nonsignificantly higher proportion in the CRP group felt recovered at day 7 compared with usual care (23.5% vs. 18.4%, p=0.53) whereas among patients with rhinosinusitis a nonsignificantly lower proportion in the CRP group felt recovered (22.4% vs. 28.9%, p=0.37).

Patient Satisfaction

Patient satisfaction was reported in two related trials of CRP testing described in detail above.[56,58] However, one was a cluster randomized factorial design study (N=431), which reported satisfaction among those exposed to receiving CRP testing (+ or – a communication intervention) compared to the combined communication alone or usual care groups (no CRP).[56] The effect of the communication intervention in both groups is likely to be to push the specific effect of CRP testing toward the null. The proportion of patients who were at least "very satisfied" was not different between groups (77% vs. 76%; unadjusted RR 1.01; 95% CI 0.91 to 1.13).[56] The second study (n=258) cluster randomized patients to CRP or no CRP, and found that more patients were at least "very satisfied" in the CRP group (76.3% vs. 63.2%; unadjusted RR 1.21; 95% CI 1.02 to 1.43).[58] This evidence is insufficient to draw conclusions due to heterogeneity of study designs.

Use of Other Diagnostic Tests

Low-strength evidence from two trials was inconsistent regarding the effect of CRP testing on the use of chest radiography (x-ray) compared with usual care.[55,179] In one trial conducted in Russia, the use of CRP testing was associated with a statistically significantly higher use of chest x-ray (76% vs. 55%; unadjusted RR 1.40, 95% CI 1.11 to 1.76).[179] The other trial conducted in the United States found non-statistically significant lower use of chest x-ray in the CRP group (5% vs. 7%; unadjusted RR 1.40, 95% CI 1.11 to 1.76).[55]

One trial (N=431) provided insufficient information to assess the strength of evidence regarding the effect of CRP testing on the use of other diagnostic testing compared with either usual care or with communication skills training.[55] The study reported on a small number of events and found no significant differences between the CRP group and usual care in the use of: blood testing (1% vs. 0%), or other tests such as spirometry or sputum analysis (2% vs. 2%). It also found no significant differences between the CRP group and communication skills training for the same outcomes, as well as for chest x-ray: chest x-ray (5% vs. 5%), blood testing (1% vs. 1%), and other tests (2% vs. 0%).

Table 17. C-reactive protein point-of-care testing interventions: Key Question 4 outcomes

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Andreeva, 2014[179] Practice N=18 Provider N=18 Patient N=179 Adults ≥18 y; first consultation for acute cough or LRTI; illness <28 days Fair quality	Cluster RCT (provider level) January 2010 – April 2010 Followup: 2 weeks	Intervention: CRP testing during consultation, with guidance on interpretation. Control: usual care (clinical assessment only). Both groups received training in acute cough/LRTI and CRP testing.	Intervention vs. Control: Patient "fully recovered": 54.5% vs. 33.3%; unadjusted RR 1.63, 95% CI 1.34 to 2.34; p=0.008. Patient "fully recovered" or "almost recovered": 91.1% vs. 92.3%; unadjusted RR 0.99, 95% CI 0.90 to 1.08; p=0.77. Use of other diagnostic testing: Chest x-ray: 76% vs. 55%; unadjusted RR 1.40, 95% CI 1.11 to 1.76; p=0.004.
Cals, 2009[56] Practice N=20 Provider N=40 Patient N=431 Adults; suspected LRTI and cough <4 weeks Fair quality	2 X 2 factorial cluster RCT (clinic level). September 2005 - March 2006 and September 2006 - March 2007. Followup: 28 days.	Intervention: *Communication skills training*: based on 11 key tasks, and elicit-provide-elicit framework. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual Care	CRP + Combination vs. Communication + Control: Reconsultation within 28 days: 34.8% vs. 30.4%; unadjusted RR 1.15, 95% CI 0.87 to 1.51; p=0.50 (p-value from model adjusted for practice level). Patient satisfaction (% at least very satisfied): 76.8% vs. 76.0%; unadjusted RR 1.01, 95% CI 0.91 to 1.13; p=0.53 (p-value from model adjusted for practice level).
Cals, 2010[58] Practice N=11 Provider N=33 Patient N=258 Adults ≥18 y; first consultation for LRTI or rhinosinusitis Fair quality	RCT (individual level). November 2007- April 2008. Followup: 28 days	Intervention: CRP testing during consultation. Clinicians advised to combine CRP results with clinical findings. Control: usual care (immediate, delayed, or no antibiotics).	Reconsultation: 25.6% vs. 17.8, unadjusted RR 1.44, 95% CI 0.89 to 2.30; p=0.13. Patient feels recovered on day 7: Overall: 22.9% vs. 24.8%, p=0.73. Rhinosinusitis: 22.4% vs. 28.9%, p=0.37 LRTI: 23.5% vs. 18.4%, p=0.53 Patient satisfaction (≥very satisfied): 76.3% vs. 63.2%, unadjusted RR 1.21, 95% CI 1.02 to 1.43; p=0.02.

Table 17. C-reactive protein point-of-care testing interventions: Key Question 4 outcomes (continued)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Cals, 2011[55] (see Cals, 2009[56])	See Cals, 2009[56]	See Cals, 2009[56] (above)	Days off of work, days (SD): Communication vs. Control: 3.35 (4.54) vs. 3.37 (3.77) Communication vs. CRP: 3.35 (4.54) vs. 3.37 (4.02) Use of other diagnostic testing: Chest x-ray: Communication vs. Control:: 5% vs. 7% Communication vs. CRP: 5% vs. 5% Blood tests: Communication vs. Control: 1% vs. 0% Communication vs. CRP: 1% vs. 1% Other (spirometry, sputum): Communication vs. Control: 2% vs. 2% Communication vs. CRP: 2% vs. 0%
Cals, 2013[57] (see Cals, 2009[56]) Patient, N=379	See Cals, 2009[56]	See Cals, 2009[56] (above)	CRP + Combination vs. Communication + Control: Office visits for RTIs during followup (mean overall followup of 3.67 years), Mean No. per patient per year (95% CI): 0.40 (0.33 to 0.47) vs. 0.56 (0.43 to 0.68), p=0.12 (p-value from model adjusted for practice level).
Diederichsen, 2000[68] Practice N=35 Provider N=35 Patient N=812 Adults and children with RTI Fair quality	RCT (individual level). January 1997- April 1997. Followup: 7 days	Intervention: CRP testing during consultation. Control: usual care (clinical assessment only).	Increased or unchanged morbidity[a] after 1 week: 12% vs. 8%, adjusted[b] OR 1.6, 95% CI 1.0 to 2.6; p=0.05.
Gonzales, 2011[80] Practice N=1 Provider N=NR Patients N=131 Adults ≥ 18 y; cough ≤ 21 days and one other acute RTI symptom Fair quality	RCT (individual level). November 2005 – March 2006. Followup: 2 to 4 weeks	Interventions: *CRP testing + algorithm:* CRP testing and clinical management algorithm to guide chest x-ray and antibiotic treatment. *Algorithm only:* Clinical management algorithm to guide chest x-ray and antibiotic treatment.	Return visits (office or ED): 40% (95% CI 28 to 52) vs. 33% (95% CI 21 to 45), p=0.46.

Table 17. C-reactive protein point-of-care testing interventions: Key Question 4 outcomes (continued)

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Little, 2013[95] Practice N=228 Provider N=372 Patient N=4,121 Patients >18 y; acute RTI (upper or lower) Fair quality	2 X 2 factorial cluster RCT (clinic level). February 2011 – May 2011. Followup: 4 weeks	Interventions: *Communication skills training*: Internet-based training in communication skills; interactive booklet; video demonstrations. *CRP testing*: testing during consultation, with guidance on interpretation. *Combination*: Communication skills training + CRP testing. Control: Usual care.	Reconsultation for new or worsening symptoms within 4 weeks: CRP + Combination vs. Communication + Control: 18.5% vs. 18.4%; adjusted RR (95% CI): 1.05 (0.78 to 1.39). CRP vs. Control: 20.3% vs. 11.8%; adjusted RR (95% CI): 1.75 (1.12 to 2.60). CRP vs. Communication: 23.5% vs. 20.3%; unadjusted RR (95% CI): 1.16 (0.99 to 1.40). Symptom severity score (1−4) 2 to 4 days after consultation, mean: CRP + Combination vs. Communication + Control: 1.79 vs. 1.79; adjusted mean difference: 0.0 (95% CI −0.09 to 0.09). CRP vs. Control: 1.70 vs. 1.75; adjusted mean difference: 0.01 (95% CI −0.12 to 0.15). CRP vs. Communication, mean (SD): 1.70 (1.00) vs. 1.81 (1.02) Resolution of symptoms rated "moderately bad" or worse (median days): CRP + Combination vs. Communication + Control: 5 vs. 5; adjusted HR: 0.93 (95% CI 0.83 to 1.04). CRP vs. Control: 5 vs. 5; adjusted HR: 0.74 (95% CI 0.74 to 1.03). CRP vs. Communication, median (IQR): 5 (3, 8) vs. 6 (3, 10)
Melbye, 1995[c180] Practice N=10 Patient N=239 Patients >18 y; "subjective complaint of: (a) pneumonia, bronchitis, or asthma, or with (b) cough, shortness of breath, or chest pain on deep inspiration". "Moderate risk of bias"	RCT (individual level). Followup: 21 days	Intervention: CRP testing at the end of consultation; algorithm to guide antibiotic prescribing, based on duration of illness and recommended CRP cut-off values. Control: Usual care.	Intervention vs. Control: Patient "substantially improved" by day 7: 45.1% vs. 41.4%; unadjusted RR (95% CI): 1.09 (0.81 to 1.47); p=0.57. Patient "substantially improved" by day 28: 72.4% vs. 67.8%; unadjusted RR (95% CI): 1.07 (0.90 to 1.27); p=0.45.

CI = confidence interval, CRP = C-reactive protein, ED = emergency department, LRTC = lower respiratory tract infection, p = p-value, RCT = randomized controlled trial, RR = relative risk, RTI = respiratory tract infection, SD = standard deviation, y = years

[a]Morbidity was not otherwise defined.

[b]Specific variables adjusted for were not specified.

[c]As reported in Aabenhus, 2014[27].

Procalcitonin Point-of-Care Testing

A good-quality systematic review provides low-strength evidence that use of procalcitonin algorithms in the primary care setting to help identify appropriate adult patients for antibiotic treatment did not significantly affect the medium number of days with limited activity (9 days in

both groups), number of days missed from work (4.9 and 4.8 days), and numbers of patients with continuing or relapsed symptoms at 28 days (30% in each) compared with usual care.

In the ED setting, no difference was found in quality of life or patient assessment of illness burden. Along with other factors, this evidence is considered insufficient because these results combine patients with CAP, exacerbations of chronic obstructive pulmonary disease and acute bronchitis.

Tympanometry Point-of-Care Testing

In a fair-quality RCT of providing physicians with results of tympanometry for children ages 3 to 36 months with suspected AOM, there was no difference between tympanometric curves (normal bilaterally, some movement bilaterally, and flat curve on either side) between groups for children who were prescribed an antibiotic (p-values 0.84, 0.14, and 0.10, respectively).[121] This evidence was indirect for measuring symptom differences between groups, and insufficient for drawing conclusions.

Viral and S. Pneumococcal (Rapid Strep Tests) Point-of-Care Testing

No evidence was found for viral and S. pneumococcal point-of-care testing.

System-Level Interventions

Three fair-quality trials of electronic clinical decisionmaking tools provide low-strength evidence of no impact on reported healthcare utilization compared with usual care. Two studies reporting ED visits within 30 days found no differences between decision support and control groups. Rates were low in both studies, for example one study of patients with pharyngitis or respiratory infection reported 0.7 percent in the intervention group and 0.5 percent in the control group (p=0.99).[103] Further, return outpatient clinical visits were similar for intervention and control groups (7.7% intervention and 11.3% control). In a study of patients with acute bronchitis, ED visits within 30 days were rare across all sites and periods (usual care, paper-based and electronic decision support; baseline and postintervention), with between 0 to 0.1 of percent patients returning across intervention or control sites.[81] Similarly, in a study of patients with acute RTI, the proportion of patients who returned within 30 days for an additional physician visit (reconsultation) was similar between intervention and control arms of their study (23% intervention and 26% control, p=0.32).[89]

Multifaceted Interventions

Five trials and three observational studies reported on clinical outcomes other than use of antibiotics or medical complications.[41,94,98,102,108,129,146,147]

Patient Satisfaction

Two studies involving multiple interventions for clinicians (e.g., education, practice profiling, academic detailing) and patient education programs provide low-strength evidence of no impact on patient satisfaction.[129,147] In a fair-quality trial conducted in the Netherlands,[129] provider group education, prescribing feedback, and patient educational material did not affect the degree of patient satisfaction despite a reduction in prescribing rates (0% vs. 0% change). Patient satisfaction was also measured in a US study in patients seen in study and control clinics for acute bronchitis 1 year after the intervention (patient education and a physician-centered quality improvement project involving education, practice profiling, and academic detailing) and

found no difference in the degree of satisfaction in a combined intervention (63% vs. 69%, p=0.15, adjusted RR 1.1; 95% CI 0.81 to 1.3).[147]

Two US studies,[41,102] evaluated the relationship between receipt of an antibiotic prescription and patient satisfaction in studies with interventions aimed at patients only. One study used a combined educational and communication intervention and found all dimensions of satisfaction were higher when an antibiotic was not prescribed (3.74 vs. 4.22; p=0.005).[41] The other study compared parents of children with AOM who received an educational intervention and watchful waiting or immediate antibiotics. Parent satisfaction was the same between groups regardless of treatment (total satisfaction score 45 for both groups).[102] This evidence is insufficient due to lack of consistency and sparseness.

Reconsultation

Two studies that evaluated how adding an information leaflet to delayed prescribing affects reconsultation had mixed results.[94,98,108] Two fair-quality US trials conducted in the same population used consultation behavior as a measure of the impact of the intervention on overall clinic visits.[94,108] In these trials, providing an information leaflet to patients as an adjunct to the use of a delayed prescription strategy led to a small but statistically significant increase in reconsultation within 1 month of initial consultation (17% vs. 11%; p=0.02). However, the rate of clinic attendance for cough within 1 month to 1 year after seeing a doctor was not different between groups. A fair-quality trial from the UK showed no difference in consultation rates in the next month among patients randomized to receive an informational leaflet or not in addition to receiving an antibiotic prescription with advice to fill if symptoms worsened (10.6% vs. 13.3%).[98] Because of the inconsistency in these findings, this evidence is insufficient to draw a conclusion.

No difference in return visits in 30 days for patients with acute bronchitis or pneumonia between intervention versus control groups was found in a large fair-quality observational US study trial involved patient education and a physician-centered quality improvement project (education, practice profiling, and academic detailing).[146] This evidence is insufficient to draw conclusions on the impact of combined patient and provider education on return office visits.

Point-of-Care Tests Combined With Other Strategies

CRP Added to Patient and Provider Education

A fair-quality observational study, the HAPPY AUDIT study (Health Alliance for Prudent Prescribing, Yield And Use of Anti-microbial Drugs In the Treatment of Respiratory Tract Infections) involving general practitioners from Spain during the winters of 2008 and 2009, found similar rates of ordering chest x-rays with either a CRP+education intervention or education-alone intervention.[157]

CRP Combined With Provider-Focused Communication Training

Symptoms

There was low-strength evidence that the combination of internet-based CRP plus enhanced communication training extends the median number of days of moderately bad symptoms compared with the control group, but not compared with use of CRP or communication training alone.[95] This evidence came from the GRACE consortium-supported trial described above which found that the median number of days of moderately bad symptoms was 5 in the control and

CRP alone groups and 6 in the communication alone and combination groups.[95] The adjusted hazard ratios for the control group compared with each of the intervention groups was 0.87 (95% CI 0.74 to 1.03) for the CRP alone group, 0.79 (95% CI 0.67 to 0.92) for the communication training group, and 0.77 (95% CI 0.65 to 0.91) for the combination group. Although the intervention groups were not directly compared with one another, it is likely they have comparable effects on resolution of moderately bad symptoms as their effects compared with the control group all indicate an increase of similar magnitude and there is considerable overlap in their confidence intervals. Although the IMPAC^{3}T trial reported that symptom scores were similar for all groups, the clinical relevance of this finding is unclear in the absence of the supporting data and information about severity.[55]

Reconsultation, Diagnostic Testing Use, Days Off Work

There was low-strength evidence that use of the combined intervention of small-group face-to-face communication training plus use of CRP testing leads to similar reconsultation rates, diagnostic testing use and days off work compared with communication training alone, CRP testing use alone and usual care.[55] These findings came from the IMPAC^{3}T trial described above.[56] Individual group results were provided (Table 18), but results of statistical testing of between-group differences were not reported. Authors noted that reconsultation rates and patient-reported time to recovery were similar for all groups, but did not comment on the comparability of the diagnostic testing usage.

Table 18. Key Question 4: Outcomes for communication training combined with CRP testing in Cals, 2011[55]

Outcome	CRP Alone (N=110)	Communication Training Alone (N=84)	Communication Training Plus CRP (N=117)	Usual Care (N=120)
Mean days off work	3.35	3.37	3.39	3.37
Average reconsultations	0.40	0.18	0.27	0.37
Chest x-ray	0.05	0.05	0.09	0.07
Blood	0.01	0.01	0.05	0.00
Other (spirometry, sputum)	0.02	0.00	0.02	0.02

CRP = C-reactive protein, N = sample size

Rapid Streptococcal Antigen Detection Test Added to a Decision Rule

There was low-strength evidence that the combination of a rapid streptococcal antigen detection test plus a decision rule has comparable effects on symptom improvement and return visits compared with use of the clinical score alone or delayed prescribing. This evidence came from an RCT that involved 48 general practitioners and triage practice nurses in general practices in south and central England who saw people ages ≥3 presenting with acute sore throat (2 weeks or less of sore throat) and an abnormal looking throat (e.g., erythema and/or pus) between October 2008 and April 2011.[91] The clinical score used was FeverPAIN, which involved offering immediate antibiotics for score ≥4, delayed antibiotics for scores of 2−3, and no antibiotics for scores of 0−1. There were no statistically significant differences between the combination of the rapid streptococcal antigen detection test plus a decision rule, the decision rule alone, or delayed prescribing in duration in days of moderately bad or worse symptoms (4 vs. 4 vs. 5) or in proportion of patients who returned within 1 month (6%, 8%, 8%) or after 1 month (16%, 12%, 15%).

Key Question 5. For patients with an acute respiratory tract infection, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding use of antibiotics for acute respiratory tract infections (clinicians and/or patients), improved shared decisionmaking regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?

Key Points

Educational Interventions

- Evidence suggested that knowledge is improved in the short-term with clinic-based interventions but evidence was more mixed for community-based interventions with longer-term followup.

Detailed Assessment

Educational Interventions

Seven RCTs (3 group or cluster randomized),[41,47,59,66,76,82,118] one non-RCT,[112] and six observational (pre-post) studies[149,160,163,173,176,177] evaluated gains in knowledge and changes in attitude of patients regarding use of antibiotics for acute RTI following education interventions. These were mostly fair-quality studies and broken down into three main groups by intervention methods. The first group was studies that used clinic-based passive interventions, pamphlets with or without waiting room posters.[41,76,112,160] Also considered with this group were two studies of video-based interventions[47,176] and one that compared video and pamphlet interventions to each other.[118] The second group was five studies of community or national campaigns, mostly using public campaigns, but not exclusively.[82,149,163,173,177] Finally there were two studies of unique interventions, one assessing preference for variations in the graphical format of information presented[59] and the other an active education program aimed at child care services workers and measuring change in parent knowledge about acute RTIs.[66] Outcomes assessed in these studies varied from surveys assessing patient or parent knowledge about when it is appropriate to use antibiotics to assessing attitudes and expectations for receiving antibiotic treatment for an acute RTI. These outcomes were considered separately, although they likely overlapped.

Overall, the evidence suggested that knowledge is improved in the short term with clinic-based interventions but evidence is more mixed for community-based interventions with longer-term followup. For example, a good-quality cluster RCT found temporal trends for improvement in knowledge in both groups studied.[76]

Evidence on the impact of educational interventions for patients (or parents) on expectations or attitudes towards antibiotic use for acute RTIs was insufficient due to inconsistency of findings across studies. No clear patterns based on population target (adult, child, all), intervention type (clinic-based vs. population-based and specific tools used), study size, or type and number of questions asked emerged. The clearest groupings are based on study design and duration. Three of five trials suggested no difference between groups while all four pre-post observational studies found changes in expectations and attitudes. A potential explanation for this difference is temporal trends in changes in attitudes towards antibiotics over time in the

general population. Clinic-based studies are typically fairly short duration, and four of six found a benefit with the intervention. In contrast two pre-post studies of longer duration public education campaigns (2−4 years) found a benefit over time, while a cluster RCT of a community-based intervention did not. Among studies that found a benefit, there was inconsistency in the magnitude of change and the meaning of specific differences between groups is unclear.

Knowledge

Evidence suggested that video-based interventions improve knowledge among urban parents, but not in the overall population targeted. A study using a 20-minute video plus a pamphlet found no difference in knowledge scores 2 months postintervention, although the subgroup of patients from urban clinics was significantly improved after the video (mean 6.02 vs. 6.92 out of 11; p=0.003).[47] The other study of a 3-minute animated video viewed in an urban ED found significant improvements in score immediately after the video (median 9 vs. 10 out of 10; p<0.001), and this improvement was maintained at 4 weeks.[118] The control group remained the same throughout (8 points) and a pamphlet group improved by 2 points immediately after the intervention (from 8 to 10 out of 10) and decreased by one point at 4 weeks.

Knowledge about appropriate use of antibiotics, including use for acute RTIs, following national or community-wide campaigns were evaluated in one good-quality cluster RCT[82] and two observational studies.[163,173] Findings from these studies suggest that the interventions did not improve parent knowledge about appropriate antibiotics use in acute RTIs. The best evidence came from a cluster RCT involved 16 communities in Massachusetts, matched for size, demographics, and other factors. The intervention (six newsletters aligned with cold and flu season over 3 years, as well as pamphlets, posters, stickers, etc. in clinic waiting rooms) was aimed at parents. Pre and postsurvey scores improved in both groups and there were no differences in the proportion answering 7 of 10 questions correctly (adjusted OR 1.2; 95% CI 0.8 to 1.7) or mean improvement in score (0.1; 95% CI −0.2 to 0.4). Regression analyses indicated that parents who had more education, were older, were white, were a stay-at-home parent, were not receiving Medicaid, and whose child was over 12 months had significantly higher odds of answering 7 or more questions correctly.

A nonrandomized prospective study of communities in Wisconsin distributed the CDC's pamphlet on antibiotic use in children, followed by nurse-led education sessions for parents at schools and day care centers.[173] Based on a four-question survey regarding awareness of the risk for antibiotic resistance, the study found that more parents in the intervention group agreed with the statements than the control group (difference 10%; 95% CI 1.9 to 18.1). Regarding appropriateness of antibiotics, both groups improved responses for colds, flu, and dry cough; neither improved for bronchitis; and only the intervention group improved for nonstreptococcal sore throat. Lastly, the study of a national campaign in England described fully in Key Question 1 evaluated general knowledge of antibiotic use and misuse and found no differences between intervention an control groups on 9 of 10 questions; a question on keeping leftover antibiotics for future use showed better improvement in the control group.[163]

A study designed to educate day care workers as a method of improving parent knowledge and attitudes towards antibiotic use found that their enrolled populations varied by the proportion with/without a college education/significantly.[66] Stratified analyses showed improved scores in the college-intervention group compared with control on overall knowledge scores (0.5 point difference on 9-point score; p<0.01), while the group without a college education showed no

difference between groups. Multivariate analysis indicated that parent characteristics of being white and having a college degree were associated with a high knowledge score (p=0.02 for each). This evidence is insufficient to draw conclusions about this intervention.

Expectations, Attitudes, Beliefs

Clinic-based interventions (videotapes, pamphlets, and posters) were mostly aimed at parents of young children. Two small trials found no impact[41,47] while a larger cluster RCT, a non-RCT (aimed at young adults), and two observational studies found that the intervention groups improved in responses to surveys of expectation for antibiotics, attitudes or beliefs towards using antibiotics, or anticipated behavior regarding use of antibiotics for acute RTIs.[76,112,160,176]

In studies of public campaigns, two pre-post studies of national campaigns that relied mainly on public campaigns reported improvement in attitudes and expectations of adults surveyed.[149,177] A study in Israel, with exposure over 4 winter months in 2 consecutive years, found that parent level of agreement with statements about appropriate antibiotic use and risks of overuse improved significantly (F=4.18, p=0.04). Further, analysis by sex of parent indicated that female parents showed more improvement than males (p=0.001). In a similar 4-year study in Australia (exposure to intervention over 3 winter months), adults were surveyed annually for 3 years about their beliefs regarding use of antibiotics for cough, colds, and flu. The study reported a decrease in the number who believe that taking antibiotics for colds and flu is appropriate (−7%, 95% CI 3.5 to 10.5). In contrast, a cluster RCT of 16 communities in Massachusetts, matched for size, demographics, and other factors found no difference between intervention and control communities in parents' expectation for antibiotics, based on three questions that included issues of satisfaction and intent to change providers.[82] The intervention (6 newsletters aligned with cold and flu season over 3 years, as well as pamphlets, posters, stickers, etc. in clinic waiting rooms) was aimed at parents.

Finally, a unique study from Norway evaluated response to varying visual displays of information about appropriate use of antibiotics for acute RTIs using a Web interface and found that compared with receiving no information, face icons and bar graphs did not lead to more subjects responding that they would not go to the doctor for a sore throat with 3 days of symptoms.[59] In fact, bar graphs and face icons of the percentage of patients with symptoms at 3 days with and without antibiotics had worse outcomes. Responses improved after subjects read detailed educational material, but even then the percent that would choose to visit the doctor at 3 was lowest in the no-visual information group.

Communication Interventions

Of the seven trials that studied interventions to improve communication between clinicians and patients regarding the use of antibiotics for acute RTIs (Appendix D), five fair-quality studies reported on various intermediate outcomes.[41,51,56,86,87] In most cases, the intermediate outcomes studied were rooted in or directly related to the theoretical model underlying the intervention and were explicitly intended outcomes of that intervention.

Two trials reported on patient enablement, self-efficacy, and intention to consult for similar illness in the future, with no significant difference found. One trial aimed at parents of children being seen in clinic for an acute RTI used an intervention based on Social Cognitive Theory.[41] This study assessed parents' self-efficacy to communicate with their child's clinician, a construct based on Social Cognitive Theory that the intervention was design to improve. The trial was a factorial design study that found parents who received the communication intervention had

higher scores than those who did not receive the communication intervention (93.47 vs. 86.28, respectively; p=0.021). In contrast, in a trial reporting on a "patient enablement score" that was not explicitly described or placed within a theoretical framework, the mean patient enablement score (scale 0−12) there was no significant difference between group scores (8.49 vs. 8.15; adjusted difference: 0.35; 95% CI −0.05 to 0.75).[51] A second study reported on "patient enablement" using a scale with a maximum score of "12",[56] but it is not clear that the two studies used the same measure. The second study also found a no significant difference in scores between the communication intervention compared with usual care, but the absolute scores were much lower (3.29 vs. 3.06; difference: 0.23; p=0.70 from an adjusted model). The same study reported on "patients' intention to consult for similar symptoms in the future", and found a lower proportion of the communication intervention group intended to consult in the future compared with usual care, although not reaching statistical significance (73.6% vs. 80.1%; p=0.16 from an adjusted model).[56]

Two trials studied interventions specifically designed to improve shared decisionmaking (Table 19), an approach in which the values, preferences and opinions of both the patient and the clinician are made explicit and considered in the decision.[86,87] The second of these shared decisionmaking trials[86] studied a revised version of the intervention used in the first trial.[87] Each trial assessed a variety of intended intermediate outcomes related to shared decisionmaking. Both studies used the Decisional Conflict Scale (scale: 1=low conflict; 5=high conflict) among patients and clinicians to assess the level of conflict the clinician or patient felt. One study reported a weak positive correlation between patient and clinician responses to the Decisional Conflict Scale (Pearson's r=0.26; p=0.06).[87] The other study compared the mean proportions of scores ≥2.5 in the intervention and control groups, reported for patients and clinicians separately.[86] There was no significant difference in the risk of decisional conflict for clinicians or patients in the interventions group compared with the control group, although the estimates were very imprecise and the point estimates were inconsistent (Table 19). Similarly, neither study found any large or statistically significant difference between an intervention group and a control group (patients or clinicians) in perceived quality of the decision (scale 1−10).[86,87] Using the Decision Regret Scale (scale 1−100), one study reported no difference in the proportion of patients with decisional regret in the intervention group compared with the control group (7% vs. 9%, respectively; p=0.91)[87] and the other study reported a slightly higher mean score in the intervention patients compared with the control patients (12.4 vs. 7.6; adjusted mean difference 4.8; 95% CI 0.9 to 8.7).[86]

This study assessed patients' adherence to their decision 2 weeks after the clinic visit and found no significant difference between intervention and control groups.[86] The same study assessed patient perceptions of how much they had participated in decisionmaking during the consultation and found that a higher proportion of patients in the intervention group compared with the control group reported having an active role in the decisionmaking process (67% vs. 49%).[86] In a subsequent publication of this study's results, the D-OPTION scale, used to measure both patient and clinician perceptions of shared decisionmaking experiences (range 0−100), was reported.[85] Patients reported significantly higher scores, while clinicians did not (Table 19). In a subgroup analysis, physicians who were also involved in medical teaching had a significant difference with the intervention versus control, although the difference appears to have been a lower score in the control group (D-Option scores 79.7 versus 73.0, respectively; p=0.001). At study exit, significantly more patients reported an active and collaborative role in

decisionmaking (as opposed to a passive role) in the intervention group than in the control group ($p<0.01$).

Both shared decisionmaking studies also assessed the intention of patients and clinicians to engage in shared decisionmaking in *future* consultations regarding the use of antibiotics for acute RTIs. Again, neither study found any large or statistically significant difference between an intervention group and a control group (patients or clinicians) in the intention to engage in shared decisionmaking in future consultations.[86,87] Finally, both studies reported on an intermediate outcome not directly related to shared decisionmaking, which was clinicians' intention to follow clinical practice guidelines regarding prescribing antibiotics for acute RTIs. Neither study found a large or statistically significant difference between an intervention group and a control group.[86,87]

Table 19. Intermediate outcomes with interventions to improve communication between clinicians and patients

Study and Characteristics	Design and Dates	Intervention and Control Details	Outcomes
Légaré, 2010[87] Practice N=4 Provider N=33 Patient N=459 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2007 – March 2008 Followup: 2 weeks	Intervention: Interactive workshops on URTIs, risk communication, fostering patient participation in decisionmaking, shared decisionmaking support tools. Control: Delayed intervention.	Difference (95% CI) Correlation of clinician and patient Decisional Conflict Scale (Pearson's *r*): 0.26 (−0.06 to 0.53), p=0.06. Quality of decision, mean score (1−10): Clinicians: 0.2 (−0.34 to 0.89), p=0.29; Patients: 0.1 (−0.88 to 0.94), p=0.57. Patients with decisional regret (%): −2 (−12 to 5), p=0.91. Intention to engage in shared decisionmaking, mean score (−3 to +3): Clinicians: 0.5 (−0.2 to 1.3), p=0.77; Patients: −0.1 (−0.6 to 0.4), p=0.16. Intention of clinicians to comply with clinical practice guidelines, mean score (−3 to +3): −0.1 (−0.7 to 0.5), p=0.58.
Légaré, 2012[86] Légaré, 2013[85] Practice N=9 Provider N=149 Patient N=359 Patients (any age); acute respiratory infection Fair quality	Parallel cluster RCT (clinic level). November 2010 – April 2011 Followup: 2 weeks	Intervention: 2-hour online tutorial and 2-hour onsite interactive workshop on decisionmaking about antibiotic treatment for RTIs and communication with patients. Control: Usual care.	Decisional Conflict Scale (% with score ≥ 2.5), adjusted RR (95% CI): Patients: 0.8 (0.2 to 2.4); Clinicians: 3.4 (0.3 to 38.0). Quality of decision (scale 1−10), mean difference (95% CI): Patients: 0.0 (−0.4 to 0.4); Clinicians: −0.2 (−0.6 to 0.2). Intent to engage in shared decisionmaking (scale −3 to +3), mean difference (95% CI): Patients: 0.2 (−0 to 0.4); Clinicians: 0.0 (95% CI −0.3 to 0.2). Patient adherence to decision (%): adjusted RR (95% CI): 1.0 (0.9 to 1.0). Patient regret over decision (scale 1−100), mean difference (95% CI): 4.8 (0.9 to 8.7). Intention of clinicians to comply with clinical practice guidelines, (scale −3 to +3), mean difference (95% CI): −0.2 (−0.5 to 0.1). D-Option Scale for shared decisionmaking (scale 0 – 100): Clinicians: 79.7 vs. 76.3; p=0.2 Patients: 80.1 vs. 74.9; p=0.001

CI = confidence interval, N = sample size, p = p-value, RCT = randomized controlled trial, RTI = respiratory tract infection

Clinical Interventions

Delayed Prescribing Strategies

No evidence was found for delayed prescribing strategies.

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

One fair-quality trial of point-of-care CRP testing reported on various intermediate outcomes[56] (Appendix D). The study was of a factorial design that assessed two interventions – one to train clinicians in the use of CRP testing and one to enhance clinicians' communication skills regarding antibiotic use for acute RTIs. This study assessed two intermediate outcomes, neither of which was directly related to any theoretical model underlying the use of CRP testing to guide decisions about antibiotic use for acute RTIs. The study reported on "patients' intention to consult for similar symptoms in the future", and found that a nonsignificantly lower proportion of the CRP testing group intended to consult in the future compared with usual care (75.4% vs. 78.9%; p=0.52 from model adjusted for communication skills training). The study also reported on "patient enablement" using a scale with a maximum score of "12", and found a nonsignificantly lower score in the CRP testing group (2.97 vs. 3.40, p=0.13 from model adjusted for communication skills training).[56]

Other Point-of-Care Tests (Procalcitonin, Viral, Rapid Strep)

No evidence was found for other point-of-care tests.

System-Level Interventions

No evidence was found for system-level interventions.

Key Question 6. What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute respiratory tract infections (e.g., increased time burden on clinicians, patients, clinic staff)?

Key Points

- Evidence was insufficient to draw conclusions about the nonclinical adverse effects of interventions to improve appropriate antibiotic prescribing.
- The estimates of the time burden associated with interventions ranged from a few minutes with several interventions to more than 10 hours and only one study actively measured time burden for clinicians to take an online training for CRP testing, communication skills, or both and found the combination to require up to 13 minutes longer. There are no estimates on the time and other resources needed to develop and deploy the interventions within a clinic or health system.

Detailed Assessment

Educational Interventions

No study of educational interventions explicitly measured adverse consequences of creating and implementing the intervention, although some discussed related issues such as lack of participation in the education program by some clinicians, or patient participants stopping the education program part way through. A few studies described the amount of time interventions required of the participants, but very few addressed the time needed for development of the educational materials. Of the studies reporting the time required for clinicians participating in educational sessions, seven were 1 to 5 hours in duration[61,73,84,99,106,131,148] and two were 1 and 2-day sessions.[114,166] There was no assessment of whether or when such sessions might need to be repeated.

For patient education, intervention times were generally kept purposefully short. Video interventions lasted 3 to 20 minutes[47,118,124,176] depending on whether they were intended to be viewed in the clinic or at home. Time required for reading educational pamphlets were reported only in two studies, reported as 5 to 15 minutes.[118,150] An interactive computer kiosk educational program took patients 9 to 45 minutes complete. Finally, child care workers were given 45-minute presentations but the time each of these participants spent subsequently educating parents was not recorded.[66,148]

Communication Interventions

None of the seven trials of interventions to improve communication between clinicians and patients explicitly measured adverse consequences of creating and implementing the intervention, although some discussed related issues such as lack of participation by some clinicians. Six trials described the amount of time the various interventions required of the participants.[41,51,56,86,87,95] Five of the trials targeted clinicians, four of which had interventions requiring between 4 hours and 10 hours of participant time:[51,56,86,87]

- Combined communication and educational intervention about prescribing guidelines required a combined total of 10 hours.[51]
- Seminars and practice with simulated patients requiring a total of 4 hours.[56]
- Three 3-hour interactive workshops on shared decisionmaking, for a total of 9 hours.[87]
- A 2-hour online tutorial and a 2-hour on-site interactive workshop, for a total of 4 hours.[86]

In contrast, a trial using an internet-based training module reported a mean time of 37.4 minutes for training.[95] This study reported that 87.0 percent of clinicians completed the communication skills training.[95] The single trial that targeted the parents of pediatric patients required seven minutes of participant time.[41]

Although these are real concerns for the feasibility of such communication training interventions, at least one trial recognized the potential counter-balancing benefit of providing continuing medical education credit for participating clinicians.[87] Another trial found that the effect of communication training on antibiotic prescribing may extend for several years, suggesting that a long-term benefit of such interventions may counter balance the time required up front.[57] In this followup study of a previously reported trial,[56] clinicians who received the communication intervention were less likely to prescribe antibiotics for subsequent acute RTIs during a mean overall followup time of 3.67 years after the intervention (26.3% vs. 39.1%;

p=0.02). Conversely, the single poor-quality trial found that the rate of antibiotic prescription among clinicians who received communication training, which decreased at 6 weeks after the intervention (from 36.4% to 29.4%), was back to the baseline rate at 12 months of followup (36.7%).

Clinical Interventions

Delayed Prescribing Strategies

The studies of clinical strategies did not specifically measure or report on increased time burden on clinicians, sustainability of intervention (e.g., adherence to algorithm), or measures of resource use associated with ordering and interpreting the test. Compared with issuing an immediate antibiotic prescription, conceivably there is at least some increase in time burden for clinicians using delayed prescribing strategies in (1) getting oriented to using a new prescribing approach, (2) explaining to patients the likely natural history of their illness and that it would probably not be helped by antibiotics, (3) providing instructions on how to decide if and when to use the prescription, and (4) fielding patients' related questions. For example, one study provided the standardized script that clinicians were asked to use when issuing a delayed prescription, which was 235 words in length and would likely require a few minutes to read to their patients.[133] Delayed antibiotic prescription strategies requiring recontact would also require increased time for clinicians and patients compared with immediate antibiotics or delayed antibiotic strategies in which the prescription was given at the time of the visit with instructions to delay or with postdating.[92] Delayed strategies requiring the patient to return for collection of the prescription would also require more patient time.[92]

For standardized decision rules, although there would likely be an initial time investment for clinicians in getting oriented to its use, how the time burden of its implementation would compare to that of the usual care process of deciding whether immediate antibiotics are needed would likely vary based on the complexity of the decision rule. For example, the sore throat decision rule utilized in the single relevant study we identified, was very simple, only including scoring of four objective indicators (e.g., cough, fever greater than 38 degrees Celsius, swollen submandibular glands, and exudate on throat or tonsils), with a requirement for antibiotic prescription in the presence of three or four indicators, and would not be expected to require much clinician time.[132]

Point-of-Care Tests

C-Reactive Protein Point-of-Care Testing

None of the nine studies of point-of-care CRP testing explicitly measured adverse consequences of creating and implementing the intervention. Four trials described the amount of time the various interventions required of the participants.[56,58,80,95] All of the trials targeted clinicians and conducted CRP training requiring between 26.5 minutes and 1.5 hours of participant time. One trial used an intervention with an internet-based training module (mean time 26.5 minutes) and a structured group meeting organized by the individual practices (required time not reported).[95] In two trials, CRP training took 30 minutes.[56,58] In the fourth trial, clinicians participated in a 1.5-hour educational seminar that included a review of evidence-based recommendations for the evaluation and treatment of acute cough illness as well as

evidence regarding the use of CRP serum levels in diagnosing pneumonia or "other antibiotic-responsive illnesses".[80]

One trial found possible long-term benefit of training clinicians in the use of CRP testing.[57] In this followup study of a previously reported trial,[56] clinicians who received the CRP test training were slightly less likely to prescribe antibiotics for subsequent acute RTIs during a mean overall followup time of 3.67 years after the intervention (30.7% vs. 35.7%; p=0.36), although the difference was not statistically significant. Of particular interest in this study was the fact that clinicians only performed CRP testing in 3.7 percent (11/294) of subsequent episodes of RTI during the followup period.

Procalcitonin Point-of-Care Testing

The five trials and two reviews of procalcitonin did not specifically measure or report on increased time burden on clinicians, sustainability of intervention (e.g., adherence to algorithm), or measures of resource use associated with ordering and interpreting the test. The studies reported a range of 1 to 4 hours for test results being reported to the clinician, depending on where and how it was processed and reported. In all studies, clinicians communicated with patients via telephone to provide instructions on antibiotic use following interpretation of the test result. In some the patients had all been given a prescription and asked to not fill it until they heard from the clinician. Those who were deemed to not need an antibiotic were asked to return the prescription by mail. While these procedures may have been study related, they do raise questions about what process is used for handling prescribing decisions when the decision is delayed until after the patient is no longer in the clinic.

System-Level Interventions

While none of the system-level intervention studies explicitly addressed potential adverse effects of implementing the interventions or reported on the time burden associated with developing, deploying or using them, one study reported a decrease in ordering in rapid streptococcal tests associated with their system-level intervention.[103] Physicians in the intervention group (29.1%) were significantly less likely to order rapid strep tests than control group (41.5%) (RR 0.75; 95% CI 0.58 to 0.97). There was no difference in the proportion of physicians in the intervention versus control groups ordering chest radiographs however (21.2% vs. 20.7% respectively; age-adjusted RR 0.98; 95% CI 0.60 to 1.62).

Multifaceted Interventions

No study using multiple interventions explicitly measured adverse consequences of the time burden used to create and implement the intervention, although some discussed dropout rates and participation rates, which may be related. Seven studies described the amount of time required by participants to engage in the intervention, undergo training sessions, or participate in site visits or workshops.[41,79,102,129,146,147,154,167,168] Times ranged from 5−10 minutes for patient-focused interventions[41,102] and anywhere from 30 minutes to 1 day for provider-focused interventions including physician education,[167] academic profiling,[146,147] evidence based training,[79] and training to implement clinical tools.[154]

Point-of-Care Tests Combined With Other Strategies

The studies of multifaceted interventions including a testing component did not specifically measure or report on measures of resource use associated with ordering and interpreting tests.

The GRACE consortium-supported RCT of CRP plus provider-focused communication training (described in Key Question 1) found that the multifaceted group had the highest time burden.[95] Briefly, the GRACE consortium-supported RCT compared internet-based training in CRP use, enhanced provider communication skills, or both in patients with URTI and LRTIs seen between February and March of 2011 across 259 primary care practices in six European countries.[95] The communication training was accompanied by video demonstrations of consultation techniques and an interactive booklet to use during consultations. Completion of training was 87.6 percent for CRP training and 87.0 percent for communication training. Mean number of minutes spent on the training Web site was statistically significantly higher for the combination training group (39.8) and the communication training group (37.4) compared with the CRP training group (26.5; p=0.003).

Discussion

Key Findings and Strength of Evidence

The key findings of this review, based on 128 unique RCTs and observational studies, as well as five reviews, most of which were fair-quality, are summarized in Tables 20, 21, and 22 below. The factors used to determine the overall strength of evidence grades are summarized in Appendix J. Changes in overall prescribing were reported in all studies, while attempts to measure changes in appropriate or inappropriate prescribing were reported in nine studies (7%), and antibiotic resistance was reported in one study. In addition to the sparseness of reporting on the outcome of appropriate prescribing, the few studies that attempted to assess appropriate prescribing had important limitations in outcome definition and ascertainment methods and lack of consistency in methods across studies. Reporting on actual use of antibiotics by the patient was also rare; only studies of delayed prescribing report patient self-report of filling the prescription, with use assumed.

Based on the direction and strength of evidence for benefits (prescribing and/or resistance) and adverse consequences (e.g. reconsultations), interventions are grouped into four categories as described in the Methods section above: (1) Interventions with evidence of improved or reduced prescribing of antibiotics and evidence of not increasing adverse consequences; (2) Interventions with evidence of improved prescribing of antibiotics and no, insufficient, or mixed evidence on adverse consequences; (3) Interventions with evidence of no effect on prescribing of antibiotics; (4) Interventions with evidence of a negative effect on prescribing of antibiotics. For all outcomes, although we sought to determine whether strategies differed based on various patient, clinical, and contextual factors, this was not possible due to the potential confounding influences of a wide variety of other factors. No intervention had high-strength evidence. Given the large number of interventions to consider, those with insufficient evidence are not discussed here.

Interventions With Evidence of Improved or Reduced Prescribing of Antibiotics and Evidence of Not Increasing Adverse Consequences

Table 20 summarizes the evidence for these interventions. Four interventions (two types of education programs, procalcitonin, and electronic decision support systems) had moderate-strength evidence for benefits and low-strength evidence for not causing adverse consequences. These interventions had the highest levels of evidence found in this report. Additionally, public education campaigns for parents had low-strength evidence for both benefits and harms.

Education Interventions

Educational interventions for parents of pediatric patients that were based in clinics (e.g., poster, pamphlet, interactive videos) were found to reduce overall antibiotic prescribing by more than 20 percent and were not found to reduce return visits for the same episode of acute RTI (N=2 RCTs). These interventions feature the ability to not only involve the child's own clinician, but also can be customized to local language and cultural needs. Evidence for the use of public education campaigns aimed at parents, combined with education interventions for clinicians, also showed some reduction in prescribing, although much smaller reductions of less than 10 percent

(N=5 RCTs). The evidence for this type of intervention shows reduction in inappropriate, or increase in appropriate prescribing (based on minimal definitions that varied by study) (N=1 RCT), and no negative impact on medical complications (N = 1 observational study) or patient satisfaction (N=2 RCTs). Data were not available on antibiotic resistance. This evidence was moderate-strength for benefits and low for harms.

Public education campaigns aimed at parents of young children (N=2 observational studies), not combined with other interventions, prescribing for AOM was significantly reduced, while diagnosis of conditions considered potential complications were not increased, and subsequent visits were decreased (N=1 observational study). The strength of this evidence was low for all outcomes.

Point-of-Care Tests

Point-of-care tests are meant to be a rapid way to determine the likelihood that a given patient has a particular type of bacterial or viral infection, or to determine if an infection is more likely to be bacterial rather viral. **Procalcitonin** was the only point-of-care test with evidence of benefit, and this benefit was restricted to adults. Use of the test in the ED or outpatient setting as a tool to assist in determining the need for an antibiotic resulting in reduced overall prescribing, with a fairly wide range in absolute reductions related to a wide variation in baseline prescribing (N=1 SR of 4 RCTs). There was no negative impact on days missing work or with limited activity, symptom duration, hospitalizations, or a combined outcome of adverse events and efficacy (N=1 RCT). Data were not available on appropriate antibiotic prescribing or on antibiotic resistance. Currently available procalcitonin tests require a number of hours, so results are not returned rapidly. This evidence as moderate-strength for benefits and low for harms.

Electronic Decision Support Systems

Electronic decision support helped to reduce antibiotic prescribing for acute RTI, although the decrease was <10 percent and reductions were associated with higher level of use of the system (i.e., used in >50% cases) (N=2 RCTs). However, there was also evidence that use of these systems can improve appropriate prescribing (N=2 RCTs) without affecting health care utilization or complications (N=1 RCT). Data were not available on antibiotic resistance. This evidence was moderate-strength for benefits and low for harms.

Table 20. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and of not causing adverse consequences

Intervention (Versus Usual Care)		Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate Absolute Change Relative Effect (Number of Studies) Strength of Evidence (SOE)	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate Absolute Change Relative Effect (Number of Studies) Strength of Evidence (SOE)	Adverse Consequences (Number Studies) Strength of Evidence (SOE)
Education	Combined patient/parent public education campaign and clinician education	Baseline: 37% to 59% (5 RCTs) Absolute change (5 RCTs): -7.3% (95% CI 4.0 to 10.6) Relative (2 RCTs): OR 0.56 (95% CI 0.36−0.87) to OR 0.62 (95% CI 0.54−0.75) (5 RCTs) SOE: **Moderate**	Reduced inappropriate prescribing: Children with pharyngitis: Baseline: 37.1% Absolute change: −10.4%; Relative: OR 0.62 (95% CI 0.54 to 0.75) Adults with acute RTIs: Baseline: 43% Absolute change: −9.7% Relative: NR (2 RCTs) SOE: **Low** Resistance: No evidence	No difference in AOM complications (1 observational study). SOE: **Low** No difference in patient or parent satisfaction (2 RCTs). SOE: **Low**
	Clinic-based education of parents of children up to age 14 years	Control: 40.8% (1 RCT) Absolute change: -21.3% (1 RCT) Relative: pooled OR 0.39 (0.26 to 0.58) (2 RCTs) SOE: **Moderate**	No evidence	No difference in return visits (2 RCTs). SOE: **Low**
	Public education campaigns for parents	Children only: Baseline: 37-44% Absolute change: NR Relative: URTI: OR 0.75 (95% CI 0.69 to 0.81) AOM: OR 0.65 (95% CI, 0.59 to 0.72) Pharyngitis: OR 0.93 (95% CI 0.89 to 0.97) (2 observational studies) SOE: **Low**	No evidence	No difference in diagnosis of complications and decrease in subsequent visits (1 observational study). SOE: **Low**

Table 20. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and of not causing adverse consequences (continued)

Intervention (Versus Usual Care)		Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate Absolute Change Relative Effect (Number of Studies) Strength of Evidence (SOE)	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate Absolute Change Relative Effect (Number of Studies) Strength of Evidence (SOE)	Adverse Consequences (Number Studies) Strength of Evidence (SOE)
Point-of-Care Tests	Procalcitonin	Adults only: Baseline: 37% to 97% Absolute: -12% to -72% Relative: Acute RTI: OR 0.14 (95% CI 0.09 to 0.22) Acute bronchitis: OR 0.15 (95% CI 0.10 to 0.23) (1 SR of 4 RCTs) SOE: **Moderate**	No evidence	No difference in number of days limited activity, missing work or continuing symptoms at 28 days for URTI or LRTI in primary care (1 RCT). No difference in AE/lack of efficacy (1 RCT) or hospitalizations (1 RCT). No difference in mortality or treatment failure at 30 days in: Acute bronchitis/ URTI in primary care or ED; URTI or LRTI in primary care (5 RCTs) SOE: **All Low**
Clinical	Electronic decision support	Systems with ≥50% use: Control group: 38% to 47% Absolute: −5% to −9% Relative: RR 0.73 (95% CI 0.58 to 0.92) (2 RCTs) SOE: **Moderate**	Improved appropriate prescribing for acute bronchitis and AOM: Baseline: 39% to 72% Absolute: −3% to −24% Relative: NR (2 RCTs) SOE: **Moderate** Resistance: No evidence	No difference in healthcare utilization or complications (1 RCT). SOE: **Low**

AE = adverse event, AOM = acute otitis media, CI = confidence interval, ED = emergency department, LRTI = lower respiratory tract infection, NA = not applicable, OR = odds ratio, URTI = upper respiratory tract infection, RCT = randomized controlled trial, RR = relative risk, SOE = strength of evidence

Note: All populations are adults and children with acute RTI unless otherwise specified.

Interventions With Evidence of Improved or Reduced Prescribing of Antibiotics and No, Insufficient, or Mixed Evidence on Adverse Consequences

Some interventions had evidence of improving prescribing, but either lacked any evidence on the impact on adverse consequences, had insufficient evidence on such outcomes, or had mixed evidence on adverse consequences (i.e., evidence of not impacting some outcomes but worsening others) (Tables 21 and 22). This evidence leaves important gaps in the evidence base and require further study. For example, rapid strep testing for sore throat, has moderate strength evidence of large reductions in overall prescribing (N=3 RCTs) and some evidence of improvement in appropriate prescribing (N=1 RCT) compared with usual care, but no evidence for other outcomes such as return visits or other adverse consequences (Table 21). Rapid multi-viral point-of-care testing in adults had low-strength evidence of improving prescribing outcomes compared

with usual care but no evidence on adverse consequences. Combining education for patients and providers with practice profiling ('audit and feedback') and academic detailing (face-to-face education specific to provider's profile) (N=3 observational studies) led to reduced prescribing for bronchitis (low-strength evidence), and evidence on reconsultation visits was insufficient (N=1 observational study).

Table 21. Interventions with evidence for improving or reducing antibiotic prescribing in acute RTI and no or insufficient evidence on adverse consequences

Intervention (Versus Usual Care)	Reduced Overall Prescribing: Baseline or Control Group Prescribing Rate Absolute Change Relative Effect (Number of Studies) Strength of Evidence (SOE)	Improved Appropriate Prescribing or Resistance: Baseline or Control Group Prescribing Rate Absolute Change Relative Effect (Number of Studies) Strength of Evidence (SOE)	Adverse Consequences Strength of Evidence (SOE)
Streptococcal antigen testing (rapid strep testing)	Baseline: 58% to 72% Absolute: −20% to −52% Relative: NR (3 RCTs) SOE: **Moderate**	Inappropriate: Baseline: 60% Absolute: −33% Relative: NR (1 RCT) SOE: **Low**	NR
Rapid viral testing (multi-viral PCR) Adults	Baseline: NR Absolute: -7.8%; p<0.01 Relative: NR (1 RCT) SOE: **Low**	NR	NR
Provider and patient education + practice profiling + academic detailing	Baseline: 21% to 88% Absolute change: Acute bronchitis: -24% to -26% Relative: NR (3 observational studies) SOE: **Low**	NR	Return clinic visits (1 observational study) SOE: **Insufficient**

NR = not reported, p = p-value, PCR = polymerase chain reaction, RCT= randomized controlled trial, SOE = strength of evidence

Note: All populations are adults and children with acute RTI unless otherwise specified.

Some other interventions had evidence of a benefit in prescribing, but also had mixed evidence on adverse consequences associated with their use (Table 22). We did not undertake determining the relative value of the various adverse consequences, such that weighing those with negative effects against those with positive or neutral effects could not be done. Depending on clinical, economic, or patient-level values, the benefits may also be considered to outweigh the adverse consequences, but again this was beyond the scope of this report.

Communication Training

Interventions to improve the ability of clinicians to communicate with patients on decisions regarding antibiotic prescribing resulted in reductions in overall prescribing that ranged from relatively small (<10%) to fairly large (over 25%) (N=5 RCTs). Evidence on reconsultations, patient satisfaction, and hospitalizations were insufficient. However, evidence on symptom improvement was conflicting – slightly longer duration of symptoms (N=3 RCTs) with the communication training group but better ratings of health at two weeks (N=1 RCT) compared with usual care (low-strength evidence).

Delayed Prescribing

There are multiple methods of implementing delayed prescribing, as well as multiple possible comparison groups. Delayed prescribing (using any method) resulted in moderate-strength evidence of large reductions in use of antibiotics, when compared to immediate prescribing (N=6 RCTs). This comparison is not the same as "usual care", where some patients will get a prescription, some will not, and some will possibly get a delayed prescription. Hence, the reductions seen based on this comparison cannot be compared to the evidence on other interventions with comparisons to usual care. A single study reported on patient-level antibiotic resistance, finding a lower rate with delayed prescribing. Although data were not available on appropriate antibiotic use, delayed prescribing also had the benefit of reducing the incidence of antibiotic associated diarrhea (N=2 RCTs). For adverse consequences, while this evidence showed no impact on reconsultations (N=4 RCTs) there was evidence of a decrease in patient satisfaction (N=5 RCTs), and an increase in persistence of symptoms (N=2 RCTs) which need to be balanced against benefits.

C-Reactive Protein (CRP)

Use of the CRP test has been shown to reduce overall prescribing for acute RTIs (N=7 RCTs), although the absolute reductions range very widely and depend in part on the baseline-prescribing rate. The evidence, however, also indicated an increase in reconsultations within 4 weeks (N=3 RCTs), but no effect on symptom resolution, or use of chest x-rays (N=2 to 4 RCTs). Evidence on the impact on hospitalizations was less clear, with five studies reporting none within 30 days, and two reporting higher frequency in the CRP groups, but not reaching statistical significance. Studies were not combinable; therefore, this evidence was low-strength for a small absolute increase in risk.

Combined Interventions

Moderate-strength evidence found that clinician communication training combined with CRP testing (N=2 RCTs) resulted in a fairly large reduction in overall prescribing (>25%) compared with usual care. One RCT reported no impact on reconsultation, diagnostic testing use, and days off work, but increased hospitalizations at 1 month (OR 4.65, 95% CI 1.21 to 17.87) and duration of symptoms. While these differences were statistically significant, the absolute differences were small (1.1% versus 0.2% hospitalization at 30 days, 5 versus 6 days symptom duration). The reasons for even a small increased risk of hospitalization were unclear in this large trial of over 4,000 patients.

Table 22. Interventions with evidence of improved prescribing for acute RTI but mixed evidence of adverse consequences

Intervention	Reduced Overall Prescribing: Baseline Prescribing Rate Absolute Change Relative Effect (Number of Studies) Strength of Evidence (SOE)	Other Benefits: Improved Appropriate Prescribing, Resistance or Reduced Adverse Effects of Antibiotics: (Number of Studies) Strength of Evidence (SOE)	Adverse Consequences (Number Studies) Strength of Evidence (SOE)
Delayed vs. immediate prescribing	Baseline: 82% to 100% Absolute: 34% to 76% Relative: OR range, 0.00 to 0.12 (6 RCTs) SOE: **Moderate**	Appropriate prescribing: No evidence. Reduced multi-drug resistance for S pneumonia strains in AOM. (1 RCT) SOE: **Low** Reduced diarrhea in AOM (2 RCTs). SOE: **Low**	No difference in reconsultation (4 RCTs). SOE: **Moderate** Reduced satisfaction (5 RCTs). SOE: **Moderate** Increased persistence of moderate to severe symptoms (2 RCTs). SOE: **Low**
CRP versus usual care	Baseline: 46% to 91% Absolute: 1.9% to 33.5% Relative: RR 0.73 (95% CI 0.60 to 0.90). (7 RCTs) SOE: **Moderate**	No evidence	Increased reconsultation within 4 weeks (3 RCTs). SOE: **Moderate** Potentially increased risk of hospitalization at 30 days: 0 events in 5 RCTs, but greater in 2 RCTs (not SS). SOE: **Low** No impact on symptom resolution (4 RCTs). SOE: **Low**
Provider communication training + CRP testing vs. usual care	Baseline: 59% Absolute: −28% Relative: OR 0.30 (95% CI 0.26 to 0.36) (2 RCTs) SOE: **Moderate**	No evidence	Increased days of moderately bad symptoms (1 RCT). Potential increased risk of hospital admissions (2 RCTs) No difference in reconsultation, diagnostic testing use, and days off work (1 RCT). SOE: **Low**
Communication training for clinicians vs. usual care	Baseline: 27%−79% (4 RCTs) Absolute: range, 9.2% to 26.1%). Relative: RR range, 0.69 to 0.17 (5 RCTs) SOE: **Moderate**	No evidence	Conflicting evidence on symptom improvement: slightly longer duration of symptoms (3 RCTs) but better ratings of health at two weeks (1 RCT). SOE: **Low**

AOM = acute otitis media, CI = confidence interval, CRP = C-Reactive protein, NA = not applicable, OR = odds ratio, RCT = randomized controlled trial, RR = relative risk, RTI = respiratory tract infection, SOE = strength of evidence, SS = statistically significant

Note: All populations are adults and children with acute RTI unless otherwise specified.

Interventions With Evidence of No Effect on Prescribing of Antibiotics

Four interventions had evidence of no impact on overall prescribing: (1) Clinic-based education for parents of children ≤24 months with AOM (N=1 RCT; moderate-strength evidence), (2) Clinician education combined with audit and feedback (N=2 RCTs; low-strength evidence), (3) Point-of-care testing for influenza in children (N=1 SR of 4 RCTs; moderate-

strength evidence), and (4) Tympanometry point-of-care testing in children (N=1 RCT, low-strength evidence). For influenza testing, this finding was not surprising as clinicians were likely using the test to confirm suspected viral illness. The lack of efficacy of a parent education program for children with AOM or clinician education combined with audit and feedback were more surprising.

Interventions With Evidence of a Negative Effect on Prescribing of Antibiotics

Evidence in children shows that use of the adult algorithm for procalcitonin results in *increased* prescribing of antibiotics and a related increase in adverse events (N=1 RCT). This suggests that procalcitonin should not be used to guide antibiotic prescribing in children without further study.

Head-to-Head Comparisons of Interventions

Single Interventions

The evidence from studies that directly compared different interventions to each other were sparse and few studies reported outcomes other than prescribing of antibiotics. Three comparisons of single interventions found little or no differences.

Delayed Prescribing Strategies

Three studies comparing different methods of delaying prescribing found no difference in effect on overall antibiotic use and similar rates of diarrhea or rash, duration of moderately bad symptoms, reconsultations, or satisfaction; but reports of vomiting and abdominal pain were more frequent with giving prescriptions with instructions to delay compared to leaving prescriptions for collection and requesting recontact, respectively (moderate-strength evidence).

Delayed Prescribing Versus Clinical Score

For sore throat, a study of a clinical score called "FeverPAIN" found a small reduction in overall prescriptions (<10%) and one fewer day of moderately bad or worse symptoms compared with delayed prescribing (low-strength evidence).

Education Versus Communication Training for Clinicians

Low-strength evidence (N=2 RCTs) found no difference in overall or appropriate antibiotic prescribing (according to guidelines) between a clinician education intervention and a clinician communication training intervention.

Communication Training for Clinicians Versus C-Reactive Protein Testing

In two similar studies using a factorial design to compare communication training for clinicians, CRP testing and the combination, the comparison of communication training (alone) and CRP testing (alone) found differing results. A more intensive communication-training program resulted in no difference in prescribing compared with CRP testing alone, while a less-intensive program resulted in a lower rate of prescribing than use of CRP testing alone. There were no differences in return clinic visits or rate of improvement of symptoms.

Augmentation of Interventions (Single Versus Two Interventions)

Communication Training for Clinicians

In a trial of communication training combined with clinician education compared with education alone, there was no difference between groups in the proportion of antibiotics that were prescribed according to guidelines for acute RTI.

Point-of-Care Tests

Limited evidence evaluating the addition of a point-of-care test to another intervention finds that the combination results in less prescribing than the single intervention.

Rapid *Streptococcus* Antigen Testing

Moderate-strength evidence found that the rapid strep test combined with a clinical score used as a decision rule (N=2 RCTs) was superior to the decision rule alone in reducing overall prescribing, but no other outcomes were studied. Low-strength evidence also found that the combination of a rapid strep test and a decision rule was superior to the decision rules alone (N=1 RCT) in reducing overall antibiotic prescribing. The combination of rapid strep testing and a clinical score was also superior in reducing overall prescribing when compared with delayed prescribing (N=1 RCT) (low-strength evidence).

C-Reactive Protein Testing

Based on two similar trials, the comparison of communication training for clinicians combined with CRP testing compared with communication alone showed a reduction in prescribing for acute RTIs; OR 0.67 (95% CI 0.56 to 0.78). The combined OR for hospitalization was 2.17 (95% CI 0.85 to 5.50), indicating a potential increase with the combined intervention, but not statistically significant. As noted above for the comparison of the combination with usual care, the reasons for the small absolute increase in risk of hospitalization were unclear in this study of over 4,000 patients. The comparison of the combination of communication training and CRP testing was not different to CRP testing alone in overall antibiotic prescribing, hospitalizations, duration of symptoms, reconsultations, days off work, or diagnostic test use. Low-strength evidence (N=1 observational study) found that adding CRP testing to patient and clinician education resulted in lower prescribing for rhinosinusitis, bronchitis, and pharyngitis. Low-strength evidence (N=1 RCT) found no difference between CRP testing combined with a clinical algorithm and the algorithm alone in overall antibiotic prescribing.

Differences in Outcomes According to Potential Moderators of Effect

Methods for Assessing Appropriate Prescribing

The methods for assessing appropriate prescribing fell into three categories: (1) ICD-9 codes or diagnostic category, (2) adherence to a specific guideline's recommendations for antibiotic use, and (3) duration of symptoms for pharyngitis or sinusitis. Although we sought to assess whether the definition of appropriateness affects the apparent effectiveness of interventions, this was not possible due to the potential confounding influences of a wide variety of other factors.

Intended Target of Intervention

The intended target of the interventions varied in the education interventions, where the reductions in prescribing were greater when the target was the patient or parent, and somewhat less when the target was the clinician or combined groups. However, direct comparisons were not available and the ranges in rates of reduction overlapped across the groups such that a clear pattern could not be established. It was clear that combining patient and clinician education did not result in clearly greater reductions. Clinical outcomes, including patient or parent satisfaction were not significantly affected. With interventions aimed at improving communication, only clinician-targeted interventions were found to have beneficial effects, although the patient-targeted evidence was very limited. Other interventions were either aimed only at clinicians (e.g., point-of-care tests), or always included both clinicians and patients (e.g., delayed prescribing).

Specific Acute Respiratory Tract Infections

The results for studies that either enrolled patients with specific acute RTIs, or reported results stratified by type of RTI, are presented in Table 23, below. Interventions with mixed results by RTI type were patient education (with evidence of effectiveness for pharyngitis but not for acute otitis media), clinician education (with evidence of effectiveness in acute otitis media and pharyngitis but not sinusitis), combined patient and clinician education (with evidence of effectiveness in bronchitis but mixed evidence for pharyngitis and sinusitis), and the addition of clinician communication training to guideline education (which was found effective for sinusitis but not for bronchitis). Three interventions were found to have a significant effect in improving antibiotic prescribing across three RTI types; electronic decision support and two multifaceted interventions. Both involved clinician and patient education, but one added CRP testing and the other added academic detailing and practice profiling. We had no evidence on the effect of other patient characteristics on any outcome (i.e., signs and symptoms [nature and duration], previous medical history [e.g., frailty, comorbidity], prior RTIs, and prior use of antibiotics, age, ethnicity, socioeconomic status, and educational level attained).

Table 23. Effectiveness of interventions in improving antibiotic prescribing by respiratory tract infection type

Intervention Category	Acute Otitis Media	Bronchitis	Pharyngitis	Sinusitis
Patient and clinician education		+	Mixed	Mixed
Patient education	-		+	
Clinician education	+		+	-
Electronic decision support	+	+	+	
Delayed prescribing	+			
CRP testing				+
Procalcitonin testing		+		
Rapid strep testing			+	
Combination of patient and provider education plus audit and feedback			-[a]	
Combination of physician education, patient education, and audit and feedback		+	+	+
Combination of physician education, patient education, and education on and access to rapid tests and CRP test		+	+	+

Table 23. Effectiveness of interventions in improving antibiotic prescribing by respiratory tract infection type (continued)

Intervention Category	Acute Otitis Media	Bronchitis	Pharyngitis	Sinusitis
Adding clinician communication training to clinician education		-		+
Adding an educational leaflet for patients to a suggestion to delay prescription filling		+		

CRP = C-reactive protein

[a]Ineffective in children with pharyngitis.

+ means at least low-strength evidence of effectiveness; - means at least low-strength evidence of ineffectiveness; blank cells mean evidence not reported by diagnosis.

Seasonal Influences

Most of the studies were timed for the season with highest prevalence of disease, mainly winter months, and no clear pattern could be discerned in the results based on this factor. Local tailoring was typically done for educational interventions (e.g., using ethnically sensitive materials). Comparisons of no tailoring versus tailoring or between degrees or methods of tailoring were not possible due to the wide variation in the combinations of specific intervention details, population, and outcome measurement across studies.

Baseline Prescribing Rates

A key background factor may be baseline prescribing rates, which varied extremely widely across studies (from a low of <10% to greater than 90%) and situations where the background prescribing was declining during the study period. While this is likely true, the poor reporting of this information severely limits the ability to analyze the potential impacts. Other background contextual factors (i.e., known patterns of disease activity [e.g., an influenza epidemic, a pertussis outbreak], or system-level characteristics) were not studied explicitly and were reported inadequately to allow analysis.

We did not find evidence on other factors as potential effect modifiers (i.e., clinician characteristics such as specialty, number of years in practice, type of clinic organization, geographic region, and population served or diagnostic method or definition used, the clinician's perception of the patient's illness severity, or the clinician's diagnostic certainty).

Findings in Relationship to What Is Already Known

There are a number of existing systematic reviews and guidelines that have contributed to our understanding of what works for targeted populations, interventions, or diseases. The reviews are generally more narrowly focused on specific types of interventions, but broadly they have concluded that multifaceted educational interventions, clinician education, delayed prescribing, CRP, and procalcitonin may be effective in certain settings.[13-16,19,38-42] Our conclusions overlap with these findings, but are not identical in that our results add evidence on more point-of-care tests and electronic decision support, as well as concluding that clinician education alone does not currently show net benefit. Reasons for these differences include the addition of a large volume of newer evidence, the use of a formal system to grade the strength of the evidence and to identify interventions with benefit and that do not cause increased adverse consequences, and the scope of interventions considered (e.g., point-of-care tests). However, a very recent systematic review of outpatient antimicrobial stewardship programs that had a broader scope

than this review (including cost outcomes, antibiotic selection outcomes, and a broader range of diagnoses) had similar findings for key interventions: education, delayed prescribing, communication training, electronic decision support, and point-of-care testing.[43] They also found that evidence on prescribing rates was mixed with audit and feedback methods.

Specific interventions that have been recommended by professional organizations and societies include delayed prescribing for children with nonsevere symptoms and persistent sinusitis (American Academy of Pediatrics), patient and family education for uncomplicated acute bronchitis (Michigan Quality Improvement Consortium [MQIC] and the American College of Chest Physicians), and rapid strep testing for pharyngitis (MQIC and the Infectious Disease Society of America). Our findings expand on the evidence used to create these recommendations.

Applicability

As planned in our protocol for this review, we focused our reporting on applicability of the body of evidence on the subgroups specified in Key Questions 1 through 4 (subquestions a through e) within the elements of the PICOTS framework.

Population Characteristics

Patients

The studies enrolled a variety of patient types, with 45 percent studying children (mean age 4 years), 27 percent studying only adults (mean age 44 years), and 28 percent studying a mixed-age population (mean age 33 years).

While 62 percent of the studies included assessments of any acute RTI, the specific infections that were most commonly studied were pharyngitis (including "sore throat" and tonsillitis) and acute otitis media. The least commonly reported infection was rhinitis. Acute bronchitis, sinusitis, and cough or common cold was studied specifically in similar proportions of studies (20% to 23%). Reporting of other patient characteristics such as previous medical history, prior RTIs, prior use of antibiotics, educational level, ethnicity, and socioeconomic status were reported in less than 20 percent of studies, such that the applicability of the body of evidence was not clear.

Clinicians

Information on clinicians studied was reported sporadically and inconsistently. While studies of acute otitis media in children typically included pediatricians and family medicine physicians, the specialty of clinicians in other studies were variably reported and very rarely analyzed. Most studies (95%) were conducted in primary care, including 14 percent in emergency departments, but few reported on clinician specialty (14%), the mean number of years of practice (13%), or population served (25%).

Intervention Characteristics

Education

Clinic-based interventions were generally locally created with similar messages but with a wide variation in the method, duration and intensity of application. Community-wide campaigns

varied in terms of the number and types of specific interventions and how they were locally tailored. All the interventions could be used in routine care in the United States.

Communication

Communication training varied from in-person to online methods and varied in intensity and duration.

Delayed Prescribing

Methods varied widely from leaving the decision to the patient, requiring the patient to return to the clinic, or other methods. All methods were likely to be in used in routine care and analysis indicated little variation in findings by method of delaying prescribing.

Point-of-Care Testing

CRP and procalcitonin interventions followed algorithms for assisting in determining the need for antibiotics. The guidance varied somewhat across studies of CRP, which may have added to the heterogeneity seen in pooled analysis. Procalcitonin algorithms were consistent across studies. Rapid viral tests included one that was multi-viral and the rest were specific for influenza. Diagnostic accuracy for rapid viral and strep tests was reported in some studies, but these were similar across studies as were the findings. The turnaround time for test results varied across these studies, with some reporting the time as minutes and others as hours.

System-Level Interventions

The interventions varied somewhat, with some using a computer decision support tool that required the clinician to access it actively, while others used a "pop-up" screen based on electronic prescribing entry. It has been suggested that systems that automatically provide decision support may be more likely to improve prescribing than those that have to be actively initiated by providers.[192]

Multifaceted Interventions

This group of studies involved a very wide range of combinations of interventions, most often including some form of education and/or communication training combined with other interventions. We stratified by number and type of interventions, but the variability limited the ability to generalize findings.

Comparators

Comparators for the interventions in this review were often usual care with very few comparing competing strategies. While a small number compared reasonable competing interventions, most studies of delayed prescribing could be described as efficacy studies because they compared to either immediate prescribing or no prescribing, rather than "usual care", which would result in a mix of immediate, no, and possibly delayed prescribing. For this report, we did not report comparisons to no prescribing as a blanket prohibition on prescribing is unlikely to be implementable in the context of US medical practice.

Outcomes

By far the most commonly reported outcome was overall prescribing of antibiotics, while the key outcomes of resistance and appropriate prescribing were reported seldom and with inconsistent definitions and methods. The outcome of overall prescribing assumed in most cases that prescriptions written or filled were used, while few studies reported on actual use (mainly the delayed prescribing studies). Numerous outcomes identified as important by key informants and Technical Expert Panel (TEP) members (e.g., quality of life, utilization of vaccines, and use of nonantibiotic treatments) were either not reported at all or rarely reported such that conclusions cannot be drawn. For the most part, studies evaluated outcomes over relatively short periods of time; typically a few months in a single season when the prevalence of the infection was the highest. Community-based interventions, such as educational programs that take time and resources to establish, reported outcomes over a period of 2 to 5 years. This time period allowed for patterns of effect to be seen. These studies often reported a clear trend towards lower antibiotic prescribing for acute RTI over time in the control groups of these studies, such that snapshots of a single season may not reflect either current effectiveness or sustainability of an intervention.

Timeframes and Settings

A drawback of the body of evidence is that 55 percent of the studies were conducted in countries outside the United States. Fifty-two percent of the studies were conducted in European countries, where some form of nationalized healthcare is common. This is an issue for two reasons; the baseline or background prescribing rate varies by country, sometimes widely, and the healthcare systems, cultural attitudes, and behaviors of clinicians and patients may vary enough in other countries to reduce the generalizability of the findings to a US population. While the relative change in an outcome may be similar across widely varying baseline rates, the ultimate outcome of reducing resistance while maintaining or improving clinical outcomes most likely requires a specific absolute reduction or a threshold of prescribing to be achieved. We found that for some interventions the relative and absolute effects were much larger when the baseline prescribing rate was very high, although this was not consistent across studies of all interventions. Related to the reasons for higher or lower baseline prescribing rates were the cultural aspects involved in prescribing for acute RTI and system-level differences in how care was provided. System-level interventions such as computer aided decision support systems are relevant to more economically developed systems, while delayed prescribing interventions effectiveness may vary depending on the typical ease of access patients have to providers and pharmacies.

The timeframe for the studies varied by the number of years and seasons studied, as noted above in our discussion of outcomes. Additionally, the years of the study may also be relevant in the situation where the background rate of prescribing antibiotics for acute RTI is declining. Older studies may have less relevance because, for example, if the prescribing rate has already declined to a low level relative to other settings or timeframes, there may be little opportunity to show an effect of an intervention.

Implications for Clinical and Policy Decisionmaking

In an effort to appropriately reduce prescribing of antibiotics for acute RTIs, clinicians and policymakers need to make choices among the relevant interventions based on the best evidence,

taking into account the characteristics of the setting in which the intervention is to be applied. Although the ultimate goal is reduction in antibiotic resistance, while not adversely affecting clinical outcomes, antibiotic resistance was understudied. Although the most logical intermediate outcome would be changes in appropriate antibiotic use, it, too, was understudied. Therefore it was necessary to consider the most widely studied, but proxy, outcome of overall prescribing to evaluate effectiveness. However, the reliability and validity of overall prescribing as a proxy for appropriate prescribing may vary because the ratio of inappropriate to appropriate prescribing can range so widely based on patient, provider and setting factors and the meaningfulness of the reductions is unclear due to a general lack of established minimally important difference parameters. Based primarily on overall prescribing, the best evidence to date supports the use of four interventions from different categories outlined in this report (education, electronic decision support, and procalcitonin). However, these interventions have varying resource use in both implementation and maintenance, and evidence on sustainability is not available. Even without considering these issues, the difficulty is that the evidence is inadequate to guide selection of the best intervention for a given setting or patient population. Among the interventions with the best evidence, however, there are some elements that could be considered in making decisions about implementation. With combined patient and clinician education programs, patient education can be simple, for example, waiting room posters featuring a letter from a local clinician. Clinician education programs should be locally tailored and the balance of program intensity and clinician participation needs to be taken into consideration. Electronic decision support systems have been shown to improve prescribing for bronchitis and acute otitis media and may be easily implementable in electronic medical record systems. The required resources to initiate a program and for clinicians to use such systems has not been studied, but ease of use (i.e. pop-up systems that do not require clinicians to seek out the information) may be key to ensuring adequate levels of use to result in benefit. For procalcitonin, while there is agreement across algorithms in terms of thresholds for antibiotic prescribing, they were developed for use in adults and use in children led to increased antibiotic use. Additional work is need to evaluate the tradeoffs in resource use required, the impact of the test turn-around time, specific populations where it is best used, and its sustainability as an intervention.

Although it is likely that combinations of interventions will result in improved results and possibly greater sustainability, the benefits and impact on resource utilization are largely unclear.

Limitations of the Review Process

Potential limitations in our process include the exclusion of non-English language publications. To explore the impact of this limitation we reviewed the English-language abstracts of studies with full text published in other languages for apparent eligibility. We identified 24 potentially relevant non-English language studies with English abstracts, of which only one was an RCT (of CRP testing) whose findings as reported in the abstract did not differ from the included studies. The remainders were mostly observational studies whose design and eligibility would require review of the full text, but none were evaluating interventions that we did not have evidence about from English-language publications. Therefore we do not believe that exclusion of non-English language studies has significantly affected the conclusions of this review. Please refer to Appendix C for citations of non-English language studies with English abstracts that were excluded from this review.

Another potential limitation involves our literature search strategies. We conducted extensive literature searches with carefully constructed electronic database strategies that underwent peer

review and multiple iterations (Appendix A). However, we found that this topic area is difficult to search for as there are no standard search terms that cover the interventions and outcomes of interest. Thus, it is possible we were unable to identify all potentially relevant studies. In our early discussions with our TEP, we established 1990 as the earliest year that studies would be relevant, but agreed upon using good-quality systematic reviews to identify studies published between 1990 and 2000 for efficiency. It is possible that in using this method we may have missed some older studies, if those reviews had not identified them. To overcome this possible limitation, we utilized our TEP members to assist in identifying missing studies by sharing our included study list with them early on, contacted manufacturers of point-of-care tests, and searched reference lists and bibliographies of included studies. Each of these methods was successful in identifying additional citations for consideration. We also note that there was limited ability to assess potential publication and reporting bias, due to the few opportunities to pool studies and the lack of availability of study protocols.

The final limitation to note is the exclusion of observational studies that did not either control for potential confounding, or were simple before-after studies without a time-series design. We established this criterion to focus our efforts on better evidence (i.e., evidence with lower risk of bias). However, in doing so, it is possible that an important study was missed. In an attempt to overcome this limitation, we allowed any form of controlling for confounding, including simple stratification of results by potential confounders.

Gaps in the Evidence Base

Several gaps and serious limitations of the evidence base limited our ability to reach strong conclusions with regard to several aspects of this review. We used the framework proposed by Robinson et al[193] to outline these limitations; classifying identified gaps as insufficient or imprecise information, biased information, inconsistency or unknown consistency, and not providing the right information. The gaps are also organized according to the PICOTS framework, by which issues relating to limitations of applicability are identified as well. These are summarized in Table 25 below. Issues pertaining to the overall body of evidence for this report include study design and conduct, the specific details of interventions, choice of comparators and more. In our sample, only 39 percent of the RCTs were cluster randomized. Since many of the interventions were applied at the level of the clinician or even the clinic, allocating the intervention at the patient level was not ideal because of the risk for contamination of samples (i.e., patients and clinicians may talk to each other about the intervention and influence outcomes). Thus, the most appropriate design for most trials of these interventions is a cluster-randomized trial. While we cannot know the direction of the bias introduced by potential contamination, it is likely that lack of clustering could reduce the observed impact of an intervention or differences between interventions.

In our review, we identified some indications for which specific interventions were beneficial or not beneficial for specific outcomes. The limitation here is that not all studies reported the outcomes stratified by such population groups, and some reported groupings of population groups that may have incorporated multiple specific indications, for example studies that stratified results by LRTI versus upper RTI. Some interventions had evidence only in one age group, for example, studies CRP testing were only available in adults.

We were limited in our ability to combine studies and to draw strong conclusions in part due to the variation in the specific details of interventions within a single category. For example, while we found multiple studies of enhancing clinician communication skills, the methods used

varied enough that combining these studies led to significant statistical heterogeneity that was not resolved with subgrouping or sensitivity analyses. Other examples are in the group of studies on clinic-based methods to educate patients or parents. These interventions varied widely, with each study representing a "one-off" intervention (e.g., videos featuring local pediatricians, videos with animation, posters of "commitment letters"). While these may be viewed as being locally tailored, they varied enough that we could not combine them, and collectively they do not provide a cohesive picture of the benefits of educating patients using a core set of principles. Unfortunately, the variation in both categories and specific details of interventions used in multifaceted intervention studies seriously prevented drawing meaningful conclusions from an area of research that is likely to hold the key to identification of the most effective intervention.

Similarly, we found that the comparisons made by studies to date are too varied to be as useful as they could be in drawing meaningful conclusions. For example, delayed prescribing as an intervention was compared with always providing a prescription in some studies and with not providing a prescription in other studies. These comparisons are less generalizable to other study designs where the comparison is to usual care or to a competing intervention. In addition, the majority of studies do make comparisons to a usual care group, with fewer studies evaluating comparisons of competing interventions.

The specific outcomes reported and how they were measured also varied and created difficulties in combining similar studies and drawing strong conclusions. A simple example is the outcomes in Key Question 1 regarding the comparative effectiveness of interventions to improve appropriate antibiotic use in acute RTIs. The biggest gap in evidence is consistent reporting resistance to antibiotics and improvement in appropriate prescribing, the two most relevant outcomes for this topic. The few studies that did report appropriate prescribing had important limitations in outcome definition and ascertainment methods and lack of consistency in methods across studies. The methods fall into three categories: ICD-9 codes or diagnostic category, adherence to a specific guideline's recommendations for antibiotic use, and duration of symptoms for pharyngitis or sinusitis. None of the studies provided detailed information on how the information was obtained or assessed. Dependence on ICD-9 codes alone is a limited approach in that patient-level characteristics that may indicate the need for antibiotic therapy are not assessed. Use of a guideline to determine appropriateness of prescribing is also limited in that the determination of whether a decision adhered to the guideline or not is subjective and requires both access to adequate patient-level data and clinical knowledge. While the duration of symptoms beyond a suggested cutoff may be an indicator for when antibiotics are needed, this information alone is inadequate to make a precise determination.

Related to either overall or appropriate prescribing outcomes, there is a gap in consistently defined goals for the necessary change or difference in prescribing that will result in meaningful benefits, such as reductions in antibiotic resistance in intervention communities. While most of the RCTs did conduct power calculations to determine adequate sample sizes, the delta used to determine these ranged widely, with no reasoning given for the selection of the difference. For example, it is not clear that a difference in antibiotic prescribing of 15 percent is enough to make differences in key outcomes such as resistance, patient outcomes, satisfaction, and resource use. Without such information, it is difficult to evaluate the magnitude of difference seen in studies even when statistically significant. Similar concerns can be raised about other outcomes. For example, symptom improvement was often measured using mean change, without any parameters for judging the importance of the change/difference (e.g., differences in change of temperature of less than one degree Fahrenheit).

The potential for increased risk of hospitalization within 1 month of the index visit found with CRP testing, communication training and the combination is concerning and deserves further scrutiny (Table 24). The evidence of potential increased risk comes largely from three trials; a single, large (N=4,264), fair-quality factorial design trial of CRP testing, communication training or the combination conducted in clinics, a smaller (N=431) study with similar design, and a small study of CRP testing only, conducted in EDs (N=139). The larger multifactorial study presented only an analysis considering CRP test use with or without communication training compared with usual care or communication training alone. After adjusting for potential confounders, this study found a non-statistically significant increased risk with use of CRP testing (22 versus 8 events). An analysis of only CRP use versus only usual care was not done. The small study of only CRP testing found a similar non-significant increased risk; however, in five other studies there were no hospitalizations in either group.

Based on events reported in the larger study, communication training also resulted in a non-statistically significant increase in risk, and the combination of the two interventions resulted in a statistically significant increased risk, although the estimates we provide are unadjusted. For the combination of CRP testing and communication training, reported in two similar multifactorial trials, we found a statistically significant increased risk, although this pooled estimate is unadjusted for potential confounders.

The reasons for a potential increased risk are unclear, since the studies were not designed to examine this outcome in depth. Since the absolute numbers of events was low, the estimates are likely to be unstable and could change with additional data.

Table 24. Risk of hospitalization at 1-month post index visit

Intervention Versus Usual Care	Study	Incidence	Relative Risk (95% Confidence Interval)
CRP Testing	Little, 2013	1% versus 0.2%	Adjusted 2.91 (0.96 to 8.85)
	Gonzales, 2011[a]	6% versus 3%	1.77 (0.34 to 9.30)
	Aabenhus, 2014	5 studies = 0 events	Not estimable
Communication Training	Little, 2013	0.5% versus 0.2%	2.35 (0.48 to 11.60)
Combination of CRP Testing and Communication Training	Little, 2013; Cals, 2011	1.1% versus 0.2%	EPC pooled (unadjusted) 4.65 (1.21 to 17.87)

CRP = C-reactive protein

[a]Not pooled due to clinical and methodological differences between studies.

For other Key Questions, the real gap is in outcome reporting in general. Few studies reported on clinical consequences of reduced prescribing, and those that did were inconsistent in definitions and methods. Studies of the rapid strep test are a good example. While it is a guideline-recommended test intended to inform prescribing decisions for moderate to severe pharyngitis, no study measured outcomes other than prescribing. No study of any intervention explicitly attempted to measure resource use. Given the clear differences in the potential for differential cost (both monetary and intangible costs) this is a major gap in understanding which intervention or combination of interventions is best in which situation. In studies that measured secondary outcomes (i.e., adverse consequences), adequate statistical power to identify statistically significant differences was uncommon. Where differences were found, it is not clear that the differences were important (clinically, economically, or from the patient's perspective).

We were limited in drawing conclusions about how the effects of the strategies may differ in specific subgroups based on previous medical history (e.g., frailty, comorbidity), prior use of antibiotics, ethnicity, socioeconomic status, clinician characteristics, and other subgroups

because studies rarely conducted subgroup analyses on these factors and these factors were not commonly reported, limiting our ability to look across studies. Due to potentially confounding influences of a wide variety of sources of variability, it is difficult to establish a relationship between any one subgroup characteristic and outcome.

With regard to settings, there is a potentially major issue with attempting to use study results from studies in settings outside the United States. There may be cultural differences that result in wide variation in baseline prescribing, the application and uptake of specific interventions, and system-level differences that make this evidence nongeneralizable to the US setting. Given that 55 percent of included studies were conducted outside the United States, this is potentially a serious limitation.

We note that we identified several good-quality systematic reviews that were related to our report topic, but we were only able to use them to crosscheck lists of included studies for two main reasons. The gaps in knowledge left by these reviews, for our purposes, were related to mainly to scope, although some were not used due to the time since literature searching was completed. For the most part the reviews included either broader populations (a wider range of diagnoses) or narrower interventions (focusing on only one intervention, or one intervention type).

Table 25. Evidence gaps for interventions to improve use of antibiotics in acute respiratory tract infections

Key Question/Outcome	Category	Evidence Gap
KQs 1 and 2: Antibiotic prescribing, use and resistance	General	Evidence of the comparative effectiveness of competing interventions is limited; the majority of studies compare to usual care with a high degree of variability in baseline prescribing across studies. Very limited evidence on comparative resistance patterns was available.
	Population	Limited evidence on effects in specific acute RTIs, particularly rhinitis. Limited evidence in older patients. CRP evidence only in adults.
	Interventions and Comparators	Evidence for most interventions was limited by variation in the specific details of interventions within a single category. Evidence on comparisons between relevant competing interventions was very limited.
	Outcomes	Few studies evaluated changes in *appropriate versus inappropriate* prescribing and there is a general lack of consensus on how to define or measure these outcomes. The studies that did attempt to report these outcomes used a wide variety of methods. Evidence on overall prescribing is limited by wide variation in ascertainment methods. There is a gap in consistently defined goals for the necessary change or difference in prescribing that will result in meaningful benefits, such as reductions in antibiotic resistance in intervention communities. Measures are typically of prescribing, rather than use of antibiotics, which may overestimate actual use. Changes in resistance to antibiotics were rarely assessed. While there appears to be a potential for increased risk of hospitalization with CRP testing and communication training, the evidence is conflicting and underpowered. A potentially important adverse consequence of antibiotic use, *clostridium difficile* infection, was not measured in these studies. Studies may have had inadequate statistical power to assess secondary outcomes - adverse consequences.
	Timing and Setting	For delayed prescribing and communication interventions, there is a gap in US-based research. The bulk of the evidence comes from outside the United States, where cultural and system-level differences may limit generalizability of findings.

Table 25. Evidence gaps for interventions to improve use of antibiotics in acute respiratory tract infections (continued)

Key Question/Outcome	Category	Evidence Gap
KQs 1 and 2: Antibiotic prescribing, use and resistance (continued)	Sources of heterogeneity	There are insufficient data to assess whether specific patient or provider characteristics, diagnostic method, or background contextual factors influence the comparative effectiveness of interventions.
KQs 3 and 4: Clinical outcomes, medical complications, healthcare utilization, and patient satisfaction	General	Evidence on clinical outcomes is very limited for most interventions (with the exception of delayed prescribing).
	Outcomes	There are large gaps in the evidence on medical complications (e.g., which are measured, how they are measured), healthcare utilization (e.g., definitions and time frames for return clinic visits, and patient satisfaction (e.g., validated methods and timing of measurement) due to inconsistent measurement and reporting.
KQ 5: Improved knowledge, improved shared decisionmaking, and improved clinician skills	General	Evidence is needed on whether or not the attainment of the intended intermediate outcomes is associated with the ultimate outcomes of interest.
KQ 6: Adverse events of interventions to improve appropriate prescribing for acute RTI	General	Information on adverse consequences of implementing interventions was completely absent.

Future Research Needs

Based on the gaps and weaknesses identified through the systematic review of the literature, the following areas present an opportunity for new research to support healthcare decisions (Table 26). Although potentially difficult and time and resource-intensive, future studies of interventions to improve antibiotic prescribing in acute RTIs should add great value to our understanding of how to best address this important public health issue by having the following methodological features:

Table 26. Future research recommendations based on evidence gaps

Evidence Gap	Recommendation
Study design and reporting	Most studies in this area can be randomized and in such cases cluster randomization should be used.
	Nonrandomized studies must adhere to the best methods, particularly using methods to control for potential confounding.
	Future systematic reviews should be comparative. Several interventions are now known to improve overall antibiotic prescribing, specifically for acute RTIs, such that the questions now include how competing interventions compare with each other. All relevant and reasonable interventions that might be considered should be included.
	To ensure better reporting of important details about methods and PICOTS characteristics, we encourage increased adherence to standardized reporting guidelines such as the TIDIER extension of CONSORT and STROBE for nonrandomized studies
Interventions and comparators	Interventions and comparators should include competing interventions from the best identified in this report, rather than designing a new intervention each time a study is undertaken. When developing new interventions, consider evidence on what has and hasn't worked to date.
	Studies of procalcitonin point-of-care tests in children with acute RTIs in primary care are needed following development of an algorithm specific to this population
	Studies comparing combined patient and clinician education, communication training, delayed prescribing, point-of-care tests, electronic decision support, and combined communication training and CRP testing should be undertaken. Delayed prescribing should also be compared with usual care.
	Studies of multifaceted interventions, using components of the interventions noted above to be effective, with adequate design and sample size, should be undertaken.
Outcome measures	The lack of consensus on how to define and measure appropriate antibiotic prescribing and use needs to be resolved. The definition needs to be clinically defensible; the ascertainment of this outcome needs to include some level of chart review. Measuring change in actual antibiotic use, rather than antibiotic prescribing only, is preferable.
	Measure resistance as an outcome. Because culture and sensitivity testing is rarely routinely performed in outpatient settings, we recognize there are major practical challenges with researching resistance including that it would require years of additional funding and long-term monitoring. However, we still recommend that, under ideal circumstances, measuring an intervention's impact on resistance would be very useful
	Measure clinical outcomes and adverse consequences of the competing interventions.
	Sustainability of interventions shown to be effective need to be studied, including what happens if and when the intervention is withdrawn and effects of time and changing baseline prescribing rates.
Analysis	Background contextual factors must be reported and considered, particularly baseline prescribing rates for particular acute RTIs.
	Patient and provider characteristics should be reported more clearly, analyzed as effect modifiers.
	Methods for studying complex interventions should be applied to future research to address issues such as intervention setting characteristics, variability of interventions across studies and time, particularly multifaceted interventions, and generalizability of interventions and results.[194]
	Multifaceted interventions should be studied as "systems" and issues of generalizability of the intervention system should be considered.

A recent report on ways to improve research evaluating antimicrobial stewardship programs echoes our findings above.[195] The authors stress that studies should move beyond measuring primarily economic outcomes and include key clinical outcomes such as resistance, incidence of adverse clinical consequences of antibiotic use, e.g. clostridium difficile in high-risk populations, should consider the difficulty in measuring outcomes that can obfuscate the findings, to consider the interventions as multifactorial, complex interventions, and the need to study the interventions in multiple settings.

Conclusions

The best evidence supports the use of specific education interventions for patients/parents and clinicians, procalcitonin in adults, and electronic decision support to reduce overall antibiotic prescribing (and in some cases improve appropriate prescribing) without causing adverse consequences, although the reduction in prescribing varied widely. Additionally, public parent education campaigns had low-strength evidence of reducing overall prescribing, not increasing diagnosis of complications and decreasing subsequent visits. Other interventions had evidence of improved prescribing but evidence on adverse consequences was lacking (streptococcal antigen testing, rapid multi-viral testing in adults), insufficient (clinician and patient education plus audit and feedback plus academic detailing) or mixed (delayed prescribing, CRP testing, clinician communication training, communication training plus CRP testing). Interventions with no impact on antibiotic prescribing were clinic-based education for parents of children ≤24 months with acute otitis media, point-of-care testing for influenza or tympanometry in children, and clinician education combined with audit and feedback. Furthermore, limited evidence suggested that using adult procalcitonin algorithms in children is not effective and results in increased antibiotic prescribing. Future studies should use a complex intervention framework and better evaluate measures of appropriate prescribing, adverse consequences such as hospitalization, sustainability, and resource use and the impact of potential effect modifiers.

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Abbreviations

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACCP	American College of Clinical Pharmacy
AHRQ	Agency for Healthcare Research & Quality
CAP	Community acquired pneumonia
CER	Comparative Effectiveness Review
CI	Confidence interval
CRP	C-reactive protein
EHC	Effective Health Care
EPC	Evidence-based Practice Center
GRACE	Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe
ICD	International Classification of Diseases
IMPAC^{3}T	Improving Management of Patients with Acute Cough by C-reactive Protein Point of Care Testing and Communication Training
LRTI	Lower respiratory tract infection
NA	Not applicable
NS	Not significant
NSD	No significant difference
OR	Odds ratio
PCR	Polymerase chain reaction
PCR	Polymerase chain reaction
RCT	Randomized controlled trial
RR	Relative risk
RTI	Respiratory tract infection
TEP	Technical Expert Panel
URTI	Upper respiratory tract infection
WBC	White blood cell
WHO	World Health Organization

Appendix A. Search Strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations[a]

1 (cold or colds or flu or influenza or virus$ or viral$ or Respiratory Syncytial Vir$ or rsv or rti or (respiratory tract$ adj3 infect$) or rhinit$ or sinusit$ or pharyngit$ or mononucleo$ or otitis media or (middle ear$ adj3 infect$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (45923)
2 (cough$ or bronchit$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3274)
3 1 and 2 (662)
4 (antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$ or antiinfective$ or anti-infective$ or anti-bacterial$ or antibacterial$).ti,ab. (21253)
5 (point of care adj5 (diagnos$ or test$ or assay$ or kit or kits)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (475)
6 (immediat$ adj5 (test$ or diagnos$)).mp. (642)
7 ((rapid$ or quick$ or swift$ or office$) adj3 (test$ or kit or kits or assay$ or swab$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1725)
8 (strep$ adj5 (test$ or kit or kits or assay$ or swab$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (206)
9 procalcitonin.mp. (286)
10 (calcitonin adj5 (precursor$ or biomarker$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3)
11 c-reactive protein$.mp. (3523)
12 monospot$.mp. (7)
13 (direct$ adj5 antibod$ adj5 stain$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (20)
14 (Fluoresc$ adj3 Antibod$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (432)
15 (reverse transcriptas$ adj5 (polymerase chain reaction$ or pcr)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1101)
16 ((singleplex$ or multiplex$) adj5 (polymerase chain reaction$ or pcr)).mp. (876)

17 ((chest$ or thorac$) adj5 (radiogra$ or x-ray$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2126)
18 ((leukocyt$ or white blood cell$ or wbc) adj3 (test$ or count$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1434)
19 (blood adj2 (gas or gases) adj5 (analy$ or test$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (336)
20 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (12448)
21 (Decision$ adj5 (make or makes or making or made)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9219)
22 ((Health or medical$) adj5 misus$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (56)
23 (Attitud$ adj5 (Health Personnel or doctor or physician or practitioner$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (186)
24 ((physician$ or doctor$ or practitioner$) adj5 (practice$ adj3 pattern$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (66)
25 ((drug$ or pharmac$) adj5 utiliz$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (624)
26 (risk$ adj3 assess$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5764)
27 (education or communication or strategy or strategies).ti,ab. (89869)
28 ((Professional$ or doctor$ or physician$ or practitioner$) adj5 patient$ adj5 (Relation$ or interaction or request$ or ask$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (677)
29 (guide$ adj3 (adheren$ or comply$ or complian$ or obey$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (580)
30 ((professional$ or clinical$) adj5 (competen$ or skill$ or abilit$ or knowledg$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2808)
31 ((inappropriat$ or imprudent$ or unreasonab$ or unwis$ or improper$ or unnecessar$ or useless$ or incorrect$ or worthless$ or useless$ or unneeded or gratuitous$ or ineffect$ or overus$ or over-us$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (254)

32 ((appropriat$ or judicious$ or judge$ or judging or wise$ or prudent$ or sensible or reasonabl$ or proper$ or necessar$ or useful$ or correct$ or worthwhile$ or needed or effectiv$ or delay$ or postpon$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (1132)
33 ((critical$ or clinical$) adj3 (path or paths or pathway$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (793)
34 ((antibiotic$ or anti-biotic$ or anti-microb$ or antimicrob$) adj3 steward$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (197)
35 (audit$ or feedback or adher$ or complian$ or train$ or educat$ or instruct$ or teach$ or taught$ or learn$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (103446)
36 ((system$ or computer$ or electronic$) adj3 (remind$ or alert$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (228)
37 ((econom$ or financ$ or dollar$ or cash or money or physician$ or provider$ or doctor$ or clinician$ or practitioner$ or nurse$) adj3 (incentiv$ or reimburs$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (445)
38 ((worker$ or job or jobs or workplace$ or employe$ or student$ or school$ or daycare or day care or pupil$ or child$ or infant$ or baby or babies or toddler$) adj5 ((keep$ or stay$ or remain$) adj3 (home or away))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9)
39 ((return$ or (com$ adj back)) adj5 (work$ or job or jobs or school$ or class or daycare or day-care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (743)
40 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (177443)
41 3 and 4 and 20 (14)
42 3 and 4 and 40 (22)
43 3 and 20 and 40 (14)
44 41 or 42 or 43 (44)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 (cold or colds or flu or influenza or virus$ or viral$ or Respiratory Syncytial Vir$ or rsv or rti or (respiratory tract$ adj3 infect$) or rhinit$ or sinusit$ or pharyngit$ or mononucleo$ or otitis media or (middle ear$ adj3 infect$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (33490)

2 (cough$ or bronchit$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6799)
3 1 and 2 (1307)
4 (antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$ or antiinfective$ or anti-infective$ or anti-bacterial$ or antibacterial$).ti,ab. (14879)
5 (point of care adj5 (diagnos$ or test$ or assay$ or kit or kits)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (180)
6 (immediat$ adj5 (test$ or diagnos$)).mp. (1278)
7 ((rapid$ or quick$ or swift$ or office$) adj3 (test$ or kit or kits or assay$ or swab$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1039)
8 (strep$ adj5 (test$ or kit or kits or assay$ or swab$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (232)
9 procalcitonin.mp. (198)
10 (calcitonin adj5 (precursor$ or biomarker$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3)
11 c-reactive protein$.mp. (5836)
12 monospot$.mp. (1)
13 (direct$ adj5 antibod$ adj5 stain$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (8)
14 (Fluoresc$ adj3 Antibod$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (411)
15 (reverse transcriptas$ adj5 (polymerase chain reaction$ or pcr)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (698)
16 ((singleplex$ or multiplex$) adj5 (polymerase chain reaction$ or pcr)).mp. (50)
17 ((chest$ or thorac$) adj5 (radiogra$ or x-ray$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1240)
18 ((leukocyt$ or white blood cell$ or wbc) adj3 (test$ or count$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (4024)
19 (blood adj2 (gas or gases) adj5 (analy$ or test$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1670)
20 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (16044)
21 (Decision$ adj5 (make or makes or making or made)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3250)
22 ((Health or medical$) adj5 misus$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (88)
23 (Attitud$ adj5 (Health Personnel or doctor or physician or practitioner$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1501)
24 ((physician$ or doctor$ or practitioner$) adj5 (practice$ adj3 pattern$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (862)
25 ((drug$ or pharmac$) adj5 utiliz$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (820)
26 (risk$ adj3 assess$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (8961)
27 (education or communication or strategy or strategies).ti,ab. (32482)

28 ((Professional$ or doctor$ or physician$ or practitioner$) adj5 patient$ adj5 (Relation$ or interaction or request$ or ask$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1853)
29 (guide$ adj3 (adheren$ or comply$ or complian$ or obey$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (930)
30 ((professional$ or clinical$) adj5 (competen$ or skill$ or abilit$ or knowledg$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3423)
31 ((inappropriat$ or imprudent$ or unreasonab$ or unwis$ or improper$ or unnecessar$ or useless$ or incorrect$ or worthless$ or useless$ or unneeded or gratuitous$ or ineffect$ or overus$ or over-us$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (191)
32 ((appropriat$ or judicious$ or judge$ or judging or wise$ or prudent$ or sensible or reasonabl$ or proper$ or necessar$ or useful$ or correct$ or worthwhile$ or needed or effectiv$ or delay$ or postpon$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (1365)
33 ((critical$ or clinical$) adj3 (path or paths or pathway$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (337)
34 ((antibiotic$ or anti-biotic$ or anti-microb$ or antimicrob$) adj3 steward$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (9)
35 (audit$ or feedback or adher$ or complian$ or train$ or educat$ or instruct$ or teach$ or taught$ or learn$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (87401)
36 ((system$ or computer$ or electronic$) adj3 (remind$ or alert$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (719)
37 ((econom$ or financ$ or dollar$ or cash or money or physician$ or provider$ or doctor$ or clinician$ or practitioner$ or nurse$) adj3 (incentiv$ or reimburs$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (312)
38 ((worker$ or job or jobs or workplace$ or employe$ or student$ or school$ or daycare or day care or pupil$ or child$ or infant$ or baby or babies or toddler$) adj5 ((keep$ or stay$ or remain$) adj3 (home or away))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (12)
39 ((return$ or (com$ adj back)) adj5 (work$ or job or jobs or school$ or class or daycare or day-care)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1035)
40 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (114217)
41 3 and 4 and 20 (22)
42 3 and 4 and 40 (61)
43 3 and 20 and 40 (27)
44 41 or 42 or 43 (84)

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1 (cold or colds or flu or influenza or virus$ or viral$ or Respiratory Syncytial Vir$ or rsv or rti or (respiratory tract$ adj3 infect$) or rhinit$ or sinusit$ or pharyngit$ or mononucleo$ or otitis

media or (middle ear$ adj3 infect$)).mp. [mp=title, abstract, full text, keywords, caption text] (1632)
2 (cough$ or bronchit$).mp. [mp=title, abstract, full text, keywords, caption text] (736)
3 1 and 2 (376)
4 (antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$ or antiinfective$ or anti-infective$ or anti-bacterial$ or antibacterial$).ti,ab. (429)
5 (point of care adj5 (diagnos$ or test$ or assay$ or kit or kits)).mp. [mp=title, abstract, full text, keywords, caption text] (19)
6 (immediat$ adj5 (test$ or diagnos$)).mp. (139)
7 ((rapid$ or quick$ or swift$ or office$) adj3 (test$ or kit or kits or assay$ or swab$)).mp. [mp=title, abstract, full text, keywords, caption text] (112)
8 (strep$ adj5 (test$ or kit or kits or assay$ or swab$)).mp. [mp=title, abstract, full text, keywords, caption text] (17)
9 procalcitonin.mp. (12)
10 (calcitonin adj5 (precursor$ or biomarker$)).mp. [mp=title, abstract, full text, keywords, caption text] (4)
11 c-reactive protein$.mp. (160)
12 monospot$.mp. (1)
13 (direct$ adj5 antibod$ adj5 stain$).mp. [mp=title, abstract, full text, keywords, caption text] (0)
14 (Fluoresc$ adj3 Antibod$).mp. [mp=title, abstract, full text, keywords, caption text] (14)
15 (reverse transcriptas$ adj5 (polymerase chain reaction$ or pcr)).mp. [mp=title, abstract, full text, keywords, caption text] (7)
16 ((singleplex$ or multiplex$) adj5 (polymerase chain reaction$ or pcr)).mp. (3)
17 ((chest$ or thorac$) adj5 (radiogra$ or x-ray$)).mp. [mp=title, abstract, full text, keywords, caption text] (258)
18 ((leukocyt$ or white blood cell$ or wbc) adj3 (test$ or count$)).mp. [mp=title, abstract, full text, keywords, caption text] (174)
19 (blood adj2 (gas or gases) adj5 (analy$ or test$)).mp. [mp=title, abstract, full text, keywords, caption text] (46)
20 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (825)
21 (Decision$ adj5 (make or makes or making or made)).mp. [mp=title, abstract, full text, keywords, caption text] (1008)
22 ((Health or medical$) adj5 misus$).mp. [mp=title, abstract, full text, keywords, caption text] (37)
23 (Attitud$ adj5 (Health Personnel or doctor or physician or practitioner$)).mp. [mp=title, abstract, full text, keywords, caption text] (30)
24 ((physician$ or doctor$ or practitioner$) adj5 (practice$ adj3 pattern$)).mp. [mp=title, abstract, full text, keywords, caption text] (43)
25 ((drug$ or pharmac$) adj5 utiliz$).mp. [mp=title, abstract, full text, keywords, caption text] (43)
26 (risk$ adj3 assess$).mp. [mp=title, abstract, full text, keywords, caption text] (5975)
27 (education or communication or strategy or strategies).ti,ab. (3246)
28 ((Professional$ or doctor$ or physician$ or practitioner$) adj5 patient$ adj5 (Relation$ or interaction or request$ or ask$)).mp. [mp=title, abstract, full text, keywords, caption text] (113)

29 (guide$ adj3 (adheren$ or comply$ or complian$ or obey$)).mp. [mp=title, abstract, full text, keywords, caption text] (133)
30 ((professional$ or clinical$) adj5 (competen$ or skill$ or abilit$ or knowledg$)).mp. [mp=title, abstract, full text, keywords, caption text] (458)
31 ((inappropriat$ or imprudent$ or unreasonab$ or unwis$ or improper$ or unnecessar$ or useless$ or incorrect$ or worthless$ or useless$ or unneeded or gratuitous$ or ineffect$ or overus$ or over-us$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (343)
32 ((appropriat$ or judicious$ or judge$ or judging or wise$ or prudent$ or sensible or reasonabl$ or proper$ or necessar$ or useful$ or correct$ or worthwhile$ or needed or effectiv$ or delay$ or postpon$) adj7 (prescri$ or ((give or gives or giving or issue or issuing or provid$) adj5 (antibiotic$ or anti-biotic$ or drug$ or pharmac$)))).mp. (484)
33 ((critical$ or clinical$) adj3 (path or paths or pathway$)).mp. [mp=title, abstract, full text, keywords, caption text] (115)
34 ((antibiotic$ or anti-biotic$ or anti-microb$ or antimicrob$) adj3 steward$).mp. [mp=title, abstract, full text, keywords, caption text] (3)
35 (audit$ or feedback or adher$ or complian$ or train$ or educat$ or instruct$ or teach$ or taught$ or learn$).mp. [mp=title, abstract, full text, keywords, caption text] (5553)
36 ((system$ or computer$ or electronic$) adj3 (remind$ or alert$)).mp. [mp=title, abstract, full text, keywords, caption text] (81)
37 ((econom$ or financ$ or dollar$ or cash or money or physician$ or provider$ or doctor$ or clinician$ or practitioner$ or nurse$) adj3 (incentiv$ or reimburs$)).mp. [mp=title, abstract, full text, keywords, caption text] (129)
38 ((worker$ or job or jobs or workplace$ or employe$ or student$ or school$ or daycare or day care or pupil$ or child$ or infant$ or baby or babies or toddler$) adj5 ((keep$ or stay$ or remain$) adj3 (home or away))).mp. [mp=title, abstract, full text, keywords, caption text] (19)
39 ((return$ or (com$ adj back)) adj5 (work$ or job or jobs or school$ or class or daycare or day-care)).mp. [mp=title, abstract, full text, keywords, caption text] (332)
40 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (7823)
41 3 and 4 and 20 (40)
42 3 and 4 and 40 (75)
43 3 and 20 and 40 (112)
44 41 or 42 or 43 (147)

Appendix B. Included Studies

Please refer to this section as a reference list for Appendixes D through I.

Primary and Companion Studies

1. Aabenhus R, Jensen JU, Jorgensen KJ, et al. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev. 2014;11:CD010130. PMID: 25374293.

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Protocols for Studies With No Published Results

1. de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, et al. Rationale, design and organization of the delayed antibiotic prescription (DAP) trial: a randomized controlled trial of the efficacy and safety of delayed antibiotic prescribing strategies in the non-complicated acute respiratory tract infections in general practice. BMC Fam Pract. 2013;14:63. PMID: 23682979.

Appendix C. Excluded Studies

The following full text articles were reviewed for inclusion but failed to meet inclusion criteria for reasons specified below.
Exclusion codes for Table C1—1: Ineligible population, 2: Ineligible intervention, 3: Ineligible comparator, 4: Ineligible outcome, 5: Ineligible setting (e.g. inpatient), 6: Ineligible study design (e.g. case report, qualitative methods), 7: Ineligible publication type (e.g. editorial letter, narrative review, etc.), 8: Outdated or ineligible systematic review, 9: Non-English language studies with English abstracts, 10: Observational studies with inadequate control for confounding and/or temporal trends.

Table C1. Excluded studies

Study	Exclusion code
1. Aagaard EM, Gonzales R, Camargo CA, Jr., et al. Physician champions are key to improving antibiotic prescribing quality. Jt Comm J Qual Patient Saf. 2010 Mar;36(3):109-16. PMID: 20235412.	4
2. Ackerman SL, Gonzales R, Stahl MS, et al. One size does not fit all: evaluating an intervention to reduce antibiotic prescribing for acute bronchitis. BMC Health Serv Res. 2013;13:462. PMID: 24188573.	6
3. Afghani B, Ngo T, Leu S-Y, et al. The effect of an interventional program on adherence to the american academy of pediatrics guidelines for palivizumab prophylaxis. Pediatr Infect Dis J. 2006 Nov;25(11):1019-24. PMID: 17072124.	3
4. Agnew J, Taaffe M, Darker C, et al. Delayed prescribing of antibiotics for respiratory tract infections: use of information leaflets. Ir Med J. 2013 Sep;106(8):243-4. PMID: 24282895.	6
5. AHRQ. Prevention of Healthcare-Associated Infections: Closing the Quality Gap: Revisiting the State of the Science. 2008.	8
6. Albanil Ballesteros MR, Calvo Rey C, Sanz Cuesta T. [Changes in antibiotics prescription in primary care]. An Esp Pediatr. 2002 Nov;57(5):420-5. PMID: 12467545.	9
7. Albrich WC, Dusemund F, Bucher B, et al. Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life": an international, multicenter poststudy survey (ProREAL). Arch Intern Med. 2012 May 14;172(9):715-22. PMID: 22782201.	6
8. Al-Khaldi YM, Al-Sharif AI, Al-Gelban KS, et al. Impact of national protocol on management of acute respiratory infections in children. Saudi Med J. 2001 Sep;22(9):780-3. PMID: 11590452.	10
9. Altiner A, Berner R, Diener A, et al. Converting habits of antibiotic prescribing for respiratory tract infections in German primary care--the cluster-randomized controlled CHANGE-2 trial. BMC Fam Pract. 2012;13:124. PMID: 23256712.	7
10. Altiner A, Wilm S, Daubener W, et al. Sputum colour for diagnosis of a bacterial infection in patients with acute cough. Scand J Prim Health Care. 2009;27(2):70-3. PMID: 19242860.	6
11. Ander AL, Eggertsen R. [Acute otitis media is not treated according to recommendations. Survey of treatment patterns in emergency centers and community health centers]. Lakartidningen. 2004 Oct 7;101(41):3142-3. PMID: 15517708.	9
12. Andrews T, Thompson M, Buckley DI, et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. PLoS ONE. 2012;7(1):e30334. PMID: 22299036.	8
13. Anonymous. No antibiotics necessary for lower respiratory infection. S Afr Fam Pract. 2005;47(7):10. PMID: CN-00557367 UPDATE.	5
14. Anonymous. No antibiotics needed for lower respiratory infection. J Fam Pract. 2005;54(9):756. PMID: CN-00569801 UPDATE.	7
15. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev. 2005(4):CD003539. PMID: 16235325.	8

Study	Exclusion code
16. Arroll B, Goodyear-Smith F, Thomas DR, et al. Delayed antibiotic prescriptions: what are the experiences and attitudes of physicians and patients? J Fam Pract. 2002 Nov;51(11):954-9. PMID: 12485551.	6
17. Arroll B, Kenealy T, Goodyear-Smith F, et al. Delayed prescriptions. BMJ. 2003 Dec 13;327(7428):1361-2. PMID: 14670853.	5
18. Ayanruoh S, Waseem M, Quee F, et al. Impact of rapid streptococcal test on antibiotic use in a pediatric emergency department. Pediatr Emerg Care. 2009 Nov;25(11):748-50. PMID: 19864964.	10
19. Ba KL, Harbarth S, Carballo S. [Procalcitonin: should it be measured systemically?]. Rev Med Suisse. 2013 Oct 16;9(402):1881-2. PMID: 24298711.	9
20. Bascelli LM, Losh DP. How does a "wait and see" approach to prescribing antibiotics for acute otitis media (AOM) compare with immediate antibiotic treatment? J Fam Pract. 2001 May;50(5):469. PMID: 11350715.	5
21. Bell DM. Promoting appropriate antimicrobial drug use: perspective from the Centers for Disease Control and Prevention. Clin Infect Dis. 2001 Sep 15;33 Suppl 3:S245-50. PMID: 11524727.	5
22. Benoni G, Zaffani S, Meneghelli G, et al. [Patologie delle alte vie respiratorie del bambino in ambulatorio: un'esperienza italiana. Diseases of the upper respiratory tract in children in ambulatory care: an Italian experience]. Pediatr Med Chir. 2005 Jan-Apr;27(1-2):67-74. PMID: 16922047.	9
23. Berild D, Abrahamsen TG, Andresen S, et al. A controlled intervention study to improve antibiotic use in a Russian paediatric hospital. Int J Antimicrob Agents. 2008 May;31(5):478-83. PMID: 18343641.	1
24. Bhavnani D, Phatinawin L, Chantra S, et al. The influence of rapid influenza diagnostic testing on antibiotic prescribing patterns in rural Thailand. Int J Infect Dis. 2007 Jul;11(4):355-9. PMID: 17324602.	3
25. Bjerrum L, Cordoba Currea GC, Llor C, et al. Lower threshold for rapid antigen detection testing in patients with sore throats would reduce antibiotic use. BMJ. 2013;347:f7055. PMID: 24286986.	7
26. Bjerrum L, Gahrn-Hansen B, Munck AP. [General practitioners who use CRP have a lower antibiotic prescribing rate to patients with sinusitis--secondary publication]. Ugeskr Laeger. 2005 Jun 20;167(25-31):2775-7. PMID: 16014265.	9
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28. Boccazzi A, Garotta M, Pontari S, et al. [Streptococcal tonsillopharyngitis: clinical vs. microbiological diagnosis]. Infez Med. 2011 Jun;19(2):100-5. PMID: 21753249.	9
29. Boonacker CWB, Hoes AW, Dikhoff M-J, et al. Interventions in health care professionals to improve treatment in children with upper respiratory tract infections. Int J Pediatr Otorhinolaryngol. 2010 Oct;74(10):1113-21. PMID: 20692051.	8
30. Boonyasiri A, Thamlikitkul V. Effectiveness of multifaceted interventions on rational use of antibiotics for patients with upper respiratory tract infections and acute diarrhea. J Med Assoc Thai. 2014 Mar;97 Suppl 3:S13-9. PMID: 24772576.	10
31. Bottaro G, Morselli I. [Epidemiology and clinical pictures of pharyngitis: report on the activity of a family paediatrician]. Pediatr Med Chir. 2007 Nov-Dec;29(6):326-30. PMID: 18410062.	9
32. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010 Feb 6;375(9713):463-74. PMID: 20097417.	1
33. Brett AS, Zuger A. The run on tamiflu--should physicians prescribe on demand? N Engl J Med. 2005 Dec 22;353(25):2636-7. PMID: 16371627.	7
34. Briel M, Young J, Tschudi P, et al. Prevalence and influence of diagnostic tests for acute respiratory tract infections in primary care. Swiss Med Wkly. 2006 Apr 15;136(15-16):248-53. PMID: 16708310.	3

Study	Exclusion code
35. Buchbinder N, Benzdira A, Belgaid A, et al. [Streptococcal pharyngitis in the pediatric emergency department: value and impact of rapid antigen detection test]. Arch Pediatr. 2007 Sep;14(9):1057-61. PMID: 17651949.	9
36. Butler CC, Rees M, Kinnersley P, et al. A case study of nurse management of upper respiratory tract infections in general practice. J Adv Nurs. 2001 Feb;33(3):328-33. PMID: 11251719.	6
37. Butler CC, Simpson SA, Dunstan F, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. BMJ. 2012;344:d8173. PMID: 22302780.	1
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39. Cao AMY, Choy JP, Mohanakrishnan LN, et al. Chest radiographs for acute lower respiratory tract infections. Cochrane Database Syst Rev. 2013;12:CD009119. PMID: 24369343.	6
40. Cardoso DM, Gilio AE, Hsin SH, et al. Impact of the rapid antigen detection test in diagnosis and treatment of acute pharyngotonsillitis in a pediatric emergency room. Rev. 2013 Jan-Mar;31(1):4-9. PMID: 23703037.	6
41. Carrat F, El Sawi A, Grandmottet G, et al. General practitioners' management of influenza with or without neuraminidase inhibitors. Eur J Gen Pract. 2007;13(3):157-9. PMID: 17853179.	3
42. Casey JR, Marsocci SM, Murphy ML, et al. White blood cell count can aid judicious antibiotic prescribing in acute upper respiratory infections in children. Clin Pediatr (Phila). 2003 Mar;42(2):113-9. PMID: 12659383.	6
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47. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med. 2006 Jul 1;174(1):84-93. PMID: 16603606.	1
48. Coco A, Vernacchio L, Horst M, et al. Management of acute otitis media after publication of the 2004 AAP and AAFP clinical practice guideline. Pediatrics. 2010 Feb;125(2):214-20. PMID: 20100746.	6
49. Cohen R, Thollot F, Lecuyer A, et al. [Impact of the rapid diagnosis downtown in the assumption of responsibility of the children in period of influenza]. Arch Pediatr. 2007 Jul;14(7):926-31. PMID: 17482437.	9
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51. Cornaglia C, Robinet J, Partouche H. [Use of Rapid Antigen Detection Test (RADT) among general practitioner teachers at the Paris Descartes University: 2005-2007]. Med Mal Infect. 2009 Jun;39(6):375-81. PMID: 19345529.	9

Study	Exclusion code
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176. Roth S, Gonzales R, Harding-Anderer T, et al. Unintended consequences of a quality measure for acute bronchitis. Am J Manag Care. 2012 Jun;18(6):e217-24. PMID: 22775073.	6
177. Rovers MM, Balemans WAF, Sanders EAM, et al. Persistence of upper respiratory tract infections in a cohort followed from childhood to adulthood. Fam Pract. 2006 Jun;23(3):286-90. PMID: 16517546.	4
178. Rubin MA, Bateman K, Donnelly S, et al. Use of a personal digital assistant for managing antibiotic prescribing for outpatient respiratory tract infections in rural communities. J Am Med Inform Assoc. 2006 Nov-Dec;13(6):627-34. PMID: 16929045.	6

Study	Exclusion code
179. Rudmik L, Hoy M, Schlosser RJ, et al. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2013 Apr;3(4):281-98. PMID: 23044832.	3
180. Sabuncu E, David J, Bernede-Bauduin C, et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. PLoS Med. 2009 Jun 2;6(6):e1000084. PMID: 19492093.	10
181. Sahini L, Tempczyk-Russell A, Agarwal R. Large-scale sequence analysis of hemagglutinin of influenza A virus identifies conserved regions suitable for targeting an anti-viral response. PLoS ONE. 2010;5(2):e9268. PMID: 20174650.	3
182. Sahlan S, Wollny A, Brockmann S, et al. Reducing unnecessary prescriptions of antibiotics for acute cough: adaptation of a leaflet aimed at Turkish immigrants in Germany. BMC Fam Pract. 2008;9:57. PMID: 18847464.	4
183. Sakkou Z, Stripeli F, Papadopoulos NG, et al. Impact of influenza infection on children's hospital admissions during two seasons in Athens, Greece. Vaccine. 2011 Feb 1;29(6):1167-72. PMID: 21172380.	2
184. Salomon J, Sommet A, Bernede C, et al. Antibiotics for nasopharyngitis are associated with a lower risk of office-based physician visit for acute otitis media within 14 days for 3- to 6-year-old children. J Eval Clin Pract. 2008 Aug;14(4):595-9. PMID: 19126177.	2
185. Santos JC, Zhang L, Zogbi HE, et al. Pneumonia during the first two years of life does not increase risk of respiratory infections in preschool children. J Infect. 2010 Jul;61(1):44-8. PMID: 20394771.	2
186. Schapowal A, Berger D, Klein P, et al. Echinacea/sage or chlorhexidine/lidocaine for treating acute sore throats: a randomized double-blind trial. Eur J Med Res. 2009 Sep 1;14(9):406-12. PMID: 19748859.	2
187. Schmelzle J, Birtwhistle RV, Tan AKW. Acute otitis media in children with tympanostomy tubes. Can Fam Physician. 2008 Aug;54(8):1123-7. PMID: 18697973.	2
188. Schouten JA, Hulscher MEJL, Trap-Liefers J, et al. Tailored interventions to improve antibiotic use for lower respiratory tract infections in hospitals: a cluster-randomized, controlled trial. Clin Infect Dis. 2007 Apr 1;44(7):931-41. PMID: 17342644.	1
189. Schroeder S, Hochreiter M, Koehler T, et al. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. Langenbecks Arch Surg. 2009 Mar;394(2):221-6. PMID: 19034493.	1
190. Schuetz P, Batschwaroff M, Dusemund F, et al. Effectiveness of a procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections outside of study conditions: a post-study survey. Eur J Clin Microbiol Infect Dis. 2010 Mar;29(3):269-77. PMID: 20039090.	2
191. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis. 2012 Sep;55(5):651-62. PMID: 22573847.	1
192. Schuetz P, Briel M, Mueller B. Clinical outcomes associated with procalcitonin algorithms to guide antibiotic therapy in respiratory tract infections. JAMA. 2013 Feb 20;309(7):717-8. PMID: 23423417.	6
193. Schwartz DB, Adler A, Dasaro AP, et al. Improving adherence with antimicrobial therapy for respiratory tract infections: a discussion of directly observed therapy (DOT) and short-course therapies. Am J Ther. 2004 Jul-Aug;11 Suppl 1:S18-21. PMID: 23570158.	3
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195. Segador J, Gil-Guillen VF, Orozco D, et al. The effect of written information on adherence to antibiotic treatment in acute sore throat. Int J Antimicrob Agents. 2005 Jul;26(1):56-61. PMID: 15961289.	3

Study	Exclusion code
196. Shaikh N, Hoberman A, Colborn DK, et al. Are nasopharyngeal cultures useful in diagnosis of acute bacterial sinusitis in children? Clin Pediatr (Phila). 2013 Dec;52(12):1118-21. PMID: 24137025.	2
197. Sharma V, Dowd MD, Slaughter AJ, et al. Effect of rapid diagnosis of influenza virus type a on the emergency department management of febrile infants and toddlers. Arch Pediatr Adolesc Med. 2002 Jan;156(1):41-3. PMID: 11772189.	4
198. Siegel RM, Kiely M, Bien JP, et al. Treatment of otitis media with observation and a safety-net antibiotic prescription. Pediatrics. 2003 Sep;112(3 Pt 1):527-31. PMID: 12949278.	6
199. Siempos II, Michalopoulos A, Falagas ME. Treatment of acute bacterial exacerbations of chronic bronchitis. Expert Opin Pharmacother. 2009 May;10(7):1173-82. PMID: 19405791.	5
200. Sih TM, Bricks LF. Optimizing the management of the main acute infections in pediatric ORL: tonsillitis, sinusitis, otitis media. Rev Bras Otorrinolaringol (Engl Ed). 2008 Sep-Oct;74(5):755-62. PMID: 19082359.	6
201. Silva B, Ferrada C, Santolaya ME. [Impact of an educational intervention on knowledge about appropriate use of antimicrobials in respiratory tract infections in adolescents]. Rev. 2012 Oct;29(5):499-503. PMID: 23282490.	9
202. Sintchenko V, Gilbert GL, Coiera E, et al. Treat or test first? Decision analysis of empirical antiviral treatment of influenza virus infection versus treatment based on rapid test results. J Clin Virol. 2002 Jul;25(1):15-21. PMID: 12126717.	4
203. Slinger R, Goldfarb D, Rajakumar D, et al. Rapid PCR detection of group A Streptococcus from flocked throat swabs: a retrospective clinical study. Ann Clin Microbiol Antimicrob. 2011;10:33. PMID: 21888649.	4
204. Smith GE, Smith S, Heatlie H, et al. What has happened to antimicrobial usage in primary care in the United Kingdom since the SMAC report? - description of trends in antimicrobial usage using the General Practice Research Database. J Public Health (Oxf). 2004 Dec;26(4):359-64. PMID: 15598854.	10
205. Smith SM. Antibiotics for acute bronchitis. 2014;3.	3
206. Soler ZM, Oyer SL, Kern RC, et al. Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations. Int Forum Allergy Rhinol. 2013 Jan;3(1):31-47. PMID: 22736403.	2
207. Soni NJ, Samson DJ, Galaydick JL, et al. Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. J Hosp Med. 2013 Sep;8(9):530-40. PMID: 23955852.	2
208. Sonnad SS, Harrison RV, Standiford CJ, et al. Issues in the development, dissemination, and effect of an evidence-based guideline for managing sore throat in adults. Jt Comm J Qual Improv. 1999 Dec;25(12):630-40. PMID: 10605653.	6
209. South M, Royle J, Starr M. A simple intervention to improve hospital antibiotic prescribing. Med J Aust. 2003 Mar 3;178(5):207-9. PMID: 12603182.	4
210. Staykova T, Black PN, Chacko EE, et al. Prophylactic antibiotic therapy for chronic bronchitis. Cochrane Database Syst Rev. 2003(1):CD004105. PMID: 12535510.	2
211. Stebbins S, Cummings DAT, Stark JH, et al. Reduction in the incidence of influenza A but not influenza B associated with use of hand sanitizer and cough hygiene in schools: a randomized controlled trial. Pediatr Infect Dis J. 2011 Nov;30(11):921-6. PMID: 21691245.	2
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213. Steinhoff MC, Walker CF, Rimoin AW, et al. A clinical decision rule for management of streptococcal pharyngitis in low-resource settings. Acta Paediatr. 2005 Aug;94(8):1038-42. PMID: 16188846.	4
214. Steinman MA, Gonzales R, Linder JA, et al. Changing use of antibiotics in community-based outpatient practice, 1991-1999.[Summary for patients in Ann Intern Med. 2003 Apr 1;138(7):I24; PMID: 12667052]. Ann Intern Med. 2003 Apr 1;138(7):525-33. PMID: 12667022.	5

Study	Exclusion code
215. Stewart J, Pilla J, Dunn L. Pilot study for appropriate anti-infective community therapy. Effect of a guideline-based strategy to optimize use of antibiotics. Can Fam Physician. 2000 Apr;46:851-9. PMID: 10790817.	10
216. Stockwell MS, Catallozzi M, Meyer D, et al. Improving care of upper respiratory infections among Latino Early Head Start parents. J Immigr Minor Health. 2010 Dec;12(6):925-31. PMID: 20157849.	10
217. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest. 2007 Jan;131(1):9-19. PMID: 17218551.	1
218. Stolz D, Christ-Crain M, Gencay MM, et al. Diagnostic value of signs, symptoms and laboratory values in lower respiratory tract infection. Swiss Med Wkly. 2006 Jul 8;136(27-28):434-40. PMID: 16862463.	4
219. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J. 2009 Dec;34(6):1364-75. PMID: 19797133.	1
220. Strumilo J, Chlabicz S, Ovhed I, et al. Management of respiratory tract infections in primary care in Poland--results of the happy audit 2 project. Przegl Epidemiol. 2014;68(1):33-8, 121-5. PMID: 25004629.	6
221. Sung L, Arroll J, Arroll B, et al. Antibiotic use for upper respiratory tract infections before and after a education campaign as reported by general practitioners in New Zealand. N Z Med J. 2006;119(1233):U1956. PMID: 16680173.	10
222. Suntarattiwong P, Sojisirikul K, Sitaposa P, et al. Clinical and epidemiological characteristics of respiratory syncytial virus and influenza virus associated hospitalization in urban Thai infants. J Med Assoc Thai. 2011 Aug;94 Suppl 3:S164-71. PMID: 22043771.	6
223. Suryaprasad A, Redd JT, Ricks PM, et al. Effect of rapid influenza diagnostic testing on antiviral treatment decisions for patients with influenza-like illness: southwestern U.S., May-December 2009. Public Health Rep. 2014 Jul-Aug;129(4):322-7. PMID: 24982534.	1
224. Svoboda P, Kantorova I, Scheer P, et al. Can procalcitonin help us in timing of re-intervention in septic patients after multiple trauma or major surgery? Hepatogastroenterology. 2007 Mar;54(74):359-63. PMID: 17523274.	1
225. Tan BK, Chandra RK, Conley DB, et al. A randomized trial examining the effect of pretreatment point-of-care computed tomography imaging on the management of patients with chronic rhinosinusitis symptoms. Int Forum Allergy Rhinol. 2011 May-Jun;1(3):229-34. PMID: 22287379.	1
226. Teng CL, Achike FI, Phua KL, et al. Modifying antibiotic prescribing: the effectiveness of academic detailing plus information leaflet in a Malaysian primary care setting. Med J Malaysia. 2006 Aug;61(3):323-31. PMID: 17240584.	10
227. Thamlikitkul V, Apisitwittaya W. Implementation of clinical practice guidelines for upper respiratory infection in Thailand. Int J Infect Dis. 2004 Jan;8(1):47-51. PMID: 14690780.	10
228. Thibeault R, Gilca R, Cote S, et al. Antibiotic use in children is not influenced by the result of rapid antigen detection test for the respiratory syncytial virus. J Clin Virol. 2007 Jul;39(3):169-74. PMID: 17532258.	4
229. Thompson PL, Gilbert RE, Long PF, et al. Has UK guidance affected general practitioner antibiotic prescribing for otitis media in children? J Public Health (Oxf). 2008 Dec;30(4):479-86. PMID: 18765405.	2
230. Thompson PL, Spyridis N, Sharland M, et al. Changes in clinical indications for community antibiotic prescribing for children in the UK from 1996 to 2006: will the new NICE prescribing guidance on upper respiratory tract infections just be ignored? Arch Dis Child. 2009 May;94(5):337-40. PMID: 19066174.	2
231. Todd J, Bertoch D, Dolan S. Use of a large national database for comparative evaluation of the effect of a bronchiolitis/viral pneumonia clinical care guideline on patient outcome and resource utilization. Arch Pediatr Adolesc Med. 2002 Nov;156(11):1086-90. PMID: 12413334.	1

Study	Exclusion code
232. Treebupachatsakul P, Tiengrim S, Thamlikitkul V. Upper respiratory tract infection in Thai adults: prevalence and prediction of bacterial causes, and effectiveness of using clinical practice guidelines. J Med Assoc Thai. 2006 Aug;89(8):1178-86. PMID: 17048427.	3
233. Tumwikirize WA, Ekwaru PJ, Mohammed K, et al. Impact of a face-to-face educational intervention on improving the management of acute respiratory infections in private pharmacies and drug shops in Uganda. East Afr Med J. 2004 Feb;Suppl:S25-32. PMID: 15125113.	3
234. Undeland DK, Kowalski TJ, Berth WL, et al. Appropriately prescribing antibiotics for patients with pharyngitis: a physician-based approach vs a nurse-only triage and treatment algorithm. Mayo Clin Proc. 2010 Nov;85(11):1011-5. PMID: 21037044.	6
235. van der Velden AW, Pijpers EJ, Kuyvenhoven MM, et al. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. Br J Gen Pract. 2012 Dec;62(605):e801-7. PMID: 23211259.	6
236. van Vugt SF, Broekhuizen BDL, Lammens C, et al. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. BMJ. 2013;346:f2450. PMID: 23633005.	4
237. Varonen H, Rautakorpi U-M, Nyberg S, et al. Implementing guidelines on acute maxillary sinusitis in general practice--a randomized controlled trial. Fam Pract. 2007 Apr;24(2):201-6. PMID: 17237494.	6
238. Venekamp RP, Rovers MM, Verheij TJM, et al. Treatment of acute rhinosinusitis: discrepancy between guideline recommendations and clinical practice. Fam Pract. 2012 Dec;29(6):706-12. PMID: 22389427.	2
239. Villasenor A, Arriaga MA, Eavey RD, et al. Educational outcomes of an otitis media workshop for primary care providers in Latin America. Otolaryngol Head Neck Surg. 1998 Mar;118(3 Pt 1):394-6. PMID: 9580113.	6
240. Vodicka TA, Thompson M, Lucas P, et al. Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. Br J Gen Pract. 2013 Jul;63(612):e445-54. PMID: 23834881.	8
241. Whyte Jt. A community health nursing approach to the problem of antibiotic over-prescribing. J Community Health Nurs. 2008 Jul-Sep;25(3):161-74. PMID: 18709577.	10
242. Wishaupt JO, Russcher A, Smeets LC, et al. Clinical impact of RT-PCR for pediatric acute respiratory infections: a controlled clinical trial. Pediatrics. 2011 Nov;128(5):e1113-20. PMID: 21987698.	3
243. Woolley SL, Bernstein JM, Davidson JA, et al. Sore throat in adults--does the introduction of a clinical scoring system improve the management of these patients in a secondary care setting? J Laryngol Otol. 2005 Jul;119(7):550-5. PMID: 16175981.	10
244. Xu M, Qin X, Astion ML, et al. Implementation of FilmArray Respiratory Viral Panel in a Core Laboratory Improves Testing Turnaround Time and Patient Care. Am J Clin Pathol. 2013 January 1, 2013;139(1):118-23. PMID: 23270907.	6
245. Zhang L, Huang J, Xu T, et al. [Procalcitonin-guided algorithms of antibiotic therapy in community-acquired lower respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials]. Chung Hua Chieh Ho Ho Hu Hsi Tsa Chih. 2012 Apr;35(4):275-82. PMID: 22781200.	9
246. Zwar N, Henderson J, Britt H, et al. Influencing antibiotic prescribing by prescriber feedback and management guidelines: a 5-year follow-up. Fam Pract. 2002 Feb;19(1):12-7. PMID: 11818344.	10

Appendix D. Data Abstraction of Randomized Controlled Trials

Note Regarding Evidence Table

Data abstractions for each included study are contained in separate rows of the evidence table (included below). Evidence rows for each study span multiple pages of this appendix document. Each study is identified in the first column of the evidence table.

Evidence Table D1. Data abstraction of randomized controlled trials

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Alder, 2005 (Please refer to Andrews, 2012 systematic review)			
Altiner, 2007 Germany Patient N = 4,918 (2,215 vs. 2,703) Provider N = 58 (28 vs. 33) Practice N = Unclear	Inclusion: Acute cough; Age ≥ 16 years; Understands German; First clinic visit for a given episode of acute cough; No other episode of cough for previous 8 weeks. Exclusion: Chronic lung disease (e.g., asthma, COPD); Immunodeficiency; "Malignant diseases".	GPs from nine regions in North-Rhine and Westphalia-Lippe, Germany. All 2,036 GPs in these regions were invited to participate.	Type: Multifaceted (Education and Communication) Targets: Clinicians and patients Description (Clinician intervention): Peer-led educational intervention addressing common clinician misunderstandings about what patients expect and want with regard to antibiotics for acute cough. Also intended to improve clinician communication through "peers motivated GPs to explore patients' expectations and demands, elicit anxieties and expectations and to make antibiotic prescribing a subject in the consultation". Description (Patient intervention): Leaflet and waiting room poster including: (1) evidence-based information about acute cough and antibiotics, (2) information about patients' role in misunderstandings about antibiotic prescriptions, and (3) message to not push for antibiotics and to decide on treatment together with doctor.
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Alder, 2005 (Please refer to Andrews, 2012 systematic review)			
Altiner, 2007 Germany Patient N = 4,918 (2,215 vs. 2,703) Provider N = 58 (28 vs. 33) Practice N = Unclear	Randomized control group physicians and patients seen by those physicians. Study was a cluster RCT, in which the control group physicians and their patients received no intervention.	Intervention group (n = 2215) vs. Control group (n= 2703) (Three subgroups each) Type of RTI (all patients): Acute cough Baseline (n = 1651, 753 vs. 898): Fever: 22.5% vs. 27.9%, p=0.31 Duration of cough before visit (days): 5.2 vs. 5.3, p=0.80 Severity of illness (range: 1 - 4): 2.1 vs. 2.2, p=0.13 When counting started for duration: NR 6 weeks (n = 1560, 675 vs. 885): Fever: 26.3% vs. 29.3%, p = 0.58 Duration of cough before visit (days): 5.4 vs. 4.8, p=0.13 Severity of illness (range: 1 - 4): 2.1 vs. 2.2, p=0.30 When counting started for duration: NR 12 months (n = 1707, 787 vs. 920): Fever: 43.5% vs. 46.6%, p=0.63 Duration of cough before visit (days): 4.1 vs. 4.4, p=0.34 Severity of illness (range: 1 - 4): 2.2 vs. 2.4, p=0.05 When counting started for duration: NR	Intervention group (n = 2215) vs. Control group (n= 2703) (Three subgroups each) Baseline (n= 1651, 753 vs. 898): Age (unclear if mean or median), y: 42.2 vs. 42.0, p=0.81 Female: 60.0% vs. 55.1%, p=0.20 Smoker: 32.6% vs. 34.9%, p=0.55 6 weeks (n = 1560, 675 vs. 885): Age (unclear if mean or median), y: 44.9 vs. 43.9, p=0.60 Female: 60.2% vs. 57.3%, p=0.41 Smoker: 28.8% vs. 33.2%, p=0.17 12 months (n = 1707, 787 vs. 920): Age (unclear if mean or median), y: 41.7 vs. 41.8, p=0.93 Female: 59.7% vs. 54.9%, p=0.22 Smoker: 29.5% vs. 31.2%, p=0.66 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Alder, 2005 (Please refer to Andrews, 2012 systematic review)			
Altiner, 2007 Germany Patient N = 4,918 (2,215 vs. 2,703) Provider N = 58 (28 vs. 33) Practice N = Unclear	Intervention group (n = 28) vs. Control group (n = 33) Specialty: General practice (both groups) Number of years in practice: NR Type of clinic: General practice (both groups) Geographical region: North-Rhine/Westphalia-Lippe, Germany (both groups) Population served: General; high, medium and low population densities (both groups) Age and % female: Both groups comparable at all three time points	Time of year: Baseline: November 2003 - January 2004; 6-week: February 2004 - April 2004; 12-month: January - March 2005. Patterns of disease activity: NR Locally tailored: Peers use a semi-standardized dialogue script. System-level characteristics: NR Other: New German law (in effect on 1/1/2004) excluded OTC symptomatic meds from reimbursement when prescribed by physician. Prior to that, cost of OTC meds was reimbursed to patient if prescribed by physician.	NR
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Alder, 2005 (Please refer to Andrews, 2012 systematic review)		
Altiner, 2007 Germany Patient N = 4,918 (2,215 vs. 2,703) Provider N = 58 (28 vs. 33) Practice N = Unclear	Percentage of patients prescribed antibiotic (Intervention group vs. control group): Baseline: 36.4% vs. 54.7% 6-week: 29.4% vs. 59.4% 12-month: 36.7% vs. 64.8% Unadjusted OR; 95% CI of antibiotic prescription at followup compared with baseline: Intervention Group: 6-week: OR=0.73; 95% CI, 0.59 to 0.88; p=0.002 12-month: OR=1.01; 95% CI, 0.84 to 1.22; p=0.931 Control group: 6-week: OR=1.22; 95% CI, 1.03 to 1.44; p=0.025 12-month: OR=1.53; 95% CI, 1.29 to 1.82, p < 0.001 Adjusted* OR; 95% CI of antibiotic prescription at followup compared with baseline: Intervention Group: 6-week: OR=0.58; 95% CI, 0.43 to 0.78; p< 0.001 12-month: OR=0.72; 95% CI, 0.54 to 0.97; p=0.028 Control group: 6-week: OR=1.52; 95% CI, 1.19 to 1.95; p=0.001 12-month: OR=1.31; 95% CI, 1.01 to 1.71 p=0.044 *Adjustment for patients' disease severity, average disease severity at practice, patients having fever, and frequency of fever in practice.	NR
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Alder, 2005 (Please refer to Andrews, 2012 systematic review)		
Altiner, 2007 Germany Patient N = 4,918 (2,215 vs. 2,703) Provider N = 58 (28 vs. 33) Practice N = Unclear	NR	NR
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Alder, 2005 (Please refer to Andrews, 2012 systematic review)			
Altiner, 2007 Germany Patient N = 4,918 (2,215 vs. 2,703) Provider N = 58 (28 vs. 33) Practice N = Unclear	NR	NR	The principal outcome was the rate of antibiotic prescription per acute cough at 6 weeks and at 12 months compared with baseline. While the same groups of clinicians were used for these analyses, the patients were different at each time period. Hence, it would be useful to have a statistical comparison of the patients seen by each group of clinicians between the time periods that were compared (i.e., comparison of intervention patients from each period; comparison of control patients from each period). The study only provided statistical comparisons between the intervention and control groups.
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)			
Baer, 2013 Switzerland Patient N = 337 Provider N = NR Practice N = 2 pediatric hospitals	All children and adolescents, 1 month to 18 years of age, presenting with LRTI to the emergency departments of two pediatric hospitals in Switzerland (Basel, Aarau) between 01/2009 and 02/2010 regardless of antibiotic treatment history	NR	Type: Clinical - POC: Procalcitonin Target: Clinicians Description: Intervention was procalcitonin (PCT) guided antibiotic treatment. Serum PCT measured by B.R.A.H.M.S. PCT sensitive Kryptor® rapid sensitive assay with functional sensitivity of 0.06 µg/L and a lower detection limit of 0.02 µg/L with an assay time of < 30 minutes. In the PCT intervention group, initiation, continuation, or termination of antibiotic treatment was strictly guided by PCT cut-off levels with the following decision categories: "definitely" (> 0.5 µg/L), "probably" (0.26-0.5 µg/L), "probably not" (0.1-0.25 µg/L), and "definitely not" (< 0.1 µg/L). Children 14 years of age or older, or care takers of children < 14 years of age, completed diary from day 1-14 on antibiotic intake, consumption or other medication, hospitalization, and symptoms. Questionnaire and visual analogue scale for self-assessment of impairment of overall daily activity thought attributable to LRTI was also distributed.
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)			
Baer, 2013 Switzerland Patient N = 337 Provider N = NR Practice N = 2 pediatric hospitals	Clinically guided standard care (control)	Type of RTI: non-CAP LRTI (36.2%) Types of Signs and Symptoms: Fever (100%), cough (99.7%), sputum production (41.8%), poor feeding (45.4%), pleuritic pain (28.2%), tachypnea (72.1%), dyspnea (64.4%), wheezing (30.0%), late inspiratory crackles (41.5%), reduced breathing sounds (32.3%) Duration of Signs and Symptoms: NR When counting started for duration: NR	Median Age: 2.8 years % female: 41.8% Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: 12.5% antibiotic pre-treatment
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)			
Baer, 2013 Switzerland Patient N = 337 Provider N = NR Practice N = 2 pediatric hospitals	Specialty: Pediatrics Number of years in practice: NR Type of clinic: Emergency department Geographical region: Basel and Aarau, Switzerland Population served: Children and adolescents	Time of year: January 2009 - February 2010 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: Study conducted at two pediatric hospitals	Appropriate use of antibiotics was determined using the following decision categories based on PCT cut-offs: "definitely" (> 0.5 µg/L), "probably" (0.26-0.5 µg/L), "probably not" (0.1-0.25 µg/L), and "definitely not" (< 0.1 µg/L)
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)		
Baer, 2013 Switzerland Patient N = 337 Provider N = NR Practice N = 2 pediatric hospitals	PCT Group (N=60) vs. Control (N=62) (Sub-group analyses) Antibiotic prescription within 14 days of randomization (reported as N (%), rate difference; (95% CI, odds ratio; 95% CI): 27 (45) vs. 10 (17), 28; 95% CI,12 to 43, OR=4.09; 95% CI, 1.80 to 9.93 Duration of antibiotic prescription (reported as mean days (medium (IQR)), mean difference; 95% CI): 2.4 (0 (0-5)) vs. 1.6 (0 (0-0)), 0.8 (-0.5, 2.0) Patients with antibiotic treatment - Other LRTI (%): D 1: 30.0 vs. 8.3 D 3: 41.7 vs. 13.3 D 5: 33.3 vs. 15.0 D 7: 15.0 vs. 13.3 D 9: 6.7 vs. 11.7 D 11: 3.3 vs. 11.7 D 13: 1.7 vs. 6.7 > D 15: 0.0 vs. 1.7	NR
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)		
Baer, 2013 Switzerland Patient N = 337 Provider N = NR Practice N = 2 pediatric hospitals	PCT Group (N=60) vs. Control (N=62) (Sub-group analyses) Antibiotic side effects (reported as N (%), rate difference; 95% CI, odds ratio; 95% CI): 14 (26) vs. 6 (10), 16; 95% CI, 1 to 30, OR=3.03; 95% CI,1.11 to 9.22 Duration of antibiotic side effects (reported as mean days (medium (IQR)), mean difference (95% CI)): 1.0 (0 (0-0.8)) vs. 0.5 (0 (0-0)), 0.5 (-0.2, 1.2) Hospitalization (reported as N (%), rate difference; 95% CI, odds ratio; 95% CI): 37 (62) vs. 32 (53), 8; 95% CI, -9 to 25), OR=1.41; 95% CI, 0.68 to 2.93 Duration of hospitalization (reported as mean days (medium (IQR)), mean difference (95% CI)): 2.5 (2 (0-4)) vs. 2.3 (1 (0-5)), 0.3 (-0.8, 1.2) Safety* (reported as N (%), rate difference; 95% CI, odds ratio; 95% CI): 15 (25) vs. 13 (22), 3; 95% CI, -12 to 18, OR=1.21; 95% CI, 0.52 to 2.85	NR
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)			
Baer, 2013 Switzerland Patient N = 337 Provider N = NR Practice N = 2 pediatric hospitals	NR	NR	* Safety includes any of the following entities: complications of LRTI, SAEs, or disease-specific failure
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Bauchner, 2006 (Please refer to Andrews, 2012 systematic review)			
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)			
Bonner, 2003 (Please refer to Doan, 2014 systematic review)			
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Bauchner, 2006 (Please refer to Andrews, 2012 systematic review)			
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)			
Bonner, 2003 (Please refer to Doan, 2014 systematic review)			
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Bauchner, 2006 (Please refer to Andrews, 2012 systematic review)			
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)			
Bonner, 2003 (Please refer to Doan, 2014 systematic review)			
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Bauchner, 2006 (Please refer to Andrews, 2012 systematic review)		
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)		
Bonner, 2003 (Please refer to Doan, 2014 systematic review)		
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Bauchner, 2006 (Please refer to Andrews, 2012 systematic review)		
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)		
Bonner, 2003 (Please refer to Doan, 2014 systematic review)		
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Bauchner, 2006 (Please refer to Andrews, 2012 systematic review)			
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)			
Bonner, 2003 (Please refer to Doan, 2014 systematic review)			
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Briel, 2006 Switzerland Patient N = 837 (259 vs. 293 vs. 285) Provider N = 45 (15 vs. 15. vs. 15) Practice N = 45 (15 vs. 15. vs. 15)	Inclusion: New-onset (within previous 28 days) acute RTI ; Age ≥ 18 years; First consultation for common cold, rhinosinusitis, pharyngitis, exudative tonsillitis, laryngitis, otitis media, bronchitis, exacerbated COPD, or influenza. Exclusion: Pneumonia; Not fluent in German; IVDA; Psychiatric disorders; Not available for phone interviews; Not able to give written informed consent.	General practitioners in two cantons, Basel-Stadt and Aargau (where self-dispensation of drugs is not allowed). All 345 GPs in these regions were invited to participate. Only one physician per participating practice.	Type: Multifaceted (Education and Communication) Target: Physicians Description: One group (n = 15) received the "Limited intervention" and one group (n = 15) received the "Full intervention". Limited intervention (Education only): The investigators developed guidelines for treatment of acute RTIs, derived from evidence-based US-guidelines and adapted to local conditions. Guidelines training included distribution of guidelines as a booklet and presentation of guidelines to physicians in an interactive 2-hour seminar. Full intervention (Education and Communication training): In addition to the Guideline training described for the Limited intervention, physicians participated in a six-hour patient-centered communication seminar in small groups and received two hours of personal feedback by phone prior to the start of the trial. Training focused on teaching physicians "how to understand and modify patients' concepts and beliefs about the use of antibiotics for acute RTIs". Physicians were taught to practice elements of active listening, to respond to emotional cues, and to tailor information given to patients. They were also introduced to a model by Prochaska and DiClemente for identifying patients' attitudes and readiness for behavior change.
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Briel, 2006 Switzerland Patient N = 837 (259 vs. 293 vs. 285) Provider N = 45 (15 vs. 15. vs. 15) Practice N = 45 (15 vs. 15. vs. 15)	Nonrandomized control group physicians and patients seen by those physicians. Study was a cluster RCT, in which the control group physicians and their patients received no intervention.	Full (n = 259) vs. Limited (n = 293) vs. Control (n = 285) Type of RTI (%): Common cold (40.9 vs. 37.5 vs. 31.9), Acute rhinosinusitis (12.7 vs. 22.5 vs. 18.6), Acute pharyngitis (7.3 vs. 8.9 vs. 15.1), Exudative tonsillitis (6.6 vs. 3.1 vs. 5.3), Acute laryngitis (2.7 vs. 1.7 vs. 3.2), Acute otitis media (2.3 vs. 2.4 vs. 1.4), Acute bronchitis (14.7 vs. 13.7 vs. 17.9), Influenza (11.2 vs. 7.9 vs. 6.0) Types of Signs and Symptoms: "Degree of discomfort" (1 - 10), median [IQR]: 5 [3] vs. 6 [3] vs. 6 [3] Duration of Signs and Symptoms (baseline): "Days with restricted activities", median [IQR]: 3 [4] vs. 4 [3] vs. 4 [3] When counting started for duration: NR	Full (n = 259) vs. Limited (n = 293) vs. Control (n = 285) Age, median [IQR]: 41.4 [22.9] vs. 43.6 [30.7] vs. 40.5 [22.8] % female: 51.4 vs. 56.7 vs. 63.9 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Briel, 2006 Switzerland Patient N = 837 (259 vs. 293 vs. 285) Provider N = 45 (15 vs. 15. vs. 15) Practice N = 45 (15 vs. 15. vs. 15)	Full (n = 15) vs. Limited (n = 15) vs. Control (n = 15) Specialty (%): General Medicine (66.7 vs. 60.0 vs. 46.7), Internal Medicine (20.0 vs. 33.3 vs. 46.7), Other (13.3 vs. 6.7 vs. 6.7) Number of years in practice, median [IQR]: 15.0 [16.8] vs. 17.2 [11.7] vs. 10.3 [17.2] Type of clinic: General practice Geographical region: Basel-Stadt and Aargau, Switzerland Population served: NR Age, median [IQR]: 50.4 [13.5] vs. 52.6 [11.9] vs. 47.8 [13.1] % women: 6.7 vs. 6.7 vs. 40.0 Previous communication training (%): 6.7 vs. 6.7 vs. 26.7	Time of year: January 2004 - May 2004 Patterns of disease activity: NR Locally tailored: No System-level characteristics: NR	Adherence to guidelines for treatment of acute RTIs developed by the investigators, derived from evidence-based US-guidelines and adapted to local conditions. The US guidelines were developed by an expert panel using a literature review and endorsed in 2001 by CDC, AAFP, ACP, and IDSA
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Briel, 2006 Switzerland Patient N = 837 (259 vs. 293 vs. 285) Provider N = 45 (15 vs. 15. vs. 15) Practice N = 45 (15 vs. 15. vs. 15)	Full Intervention vs. Limited Intervention vs. Control Antibiotics prescribed (reported by pharmacists): 13.5% vs. 15.7% vs. 21.4% Percent difference (Full vs. Limited): -2.2; 95% CI, -12.2 to 7.8 Adjusted* OR (Full vs. Limited): OR=0.86; 95% CI, 0.40 to 1.93 Antibiotics prescribed (reported by physicians): 15.1% vs. 16.7% vs. 25.6% Adjusted* OR (Full vs. Limited): OR=0.90; 95% CI, 0.44 to1.98 Antibiotics prescribed according to guidelines (as % of prescribed antibiotics): 53.8% vs. 53.1% vs. 41.1% Adjusted* OR (Full vs. Limited): OR=1.03; 95% CI, 0.30 to 3.09 Antibiotics prescribed per diagnosis, (1) % with diagnosis prescribed antibiotic; (2) % of prescriptions according to guidelines: Common cold: (1) 3.8 vs. 0.0 vs. 1.1; (2) 25.0 vs. NA vs. 0.0 Acute rhinosinusitis: (1) 21.2 vs. 37.9 vs. 49.1; (2) 57.1 vs. 64.0 vs. 65.4 Acute pharyngitis: (1) 10.5 vs. 3.8 vs. 14.0; (2) 0.0 vs. 100.0 vs. 33.3 Acute exudative tonsillitis: (1) 64.7 vs. 66.7 vs. 86.7; (2) 81.8 vs. 66.7 vs. 53.8 Acute laryngitis: (1) 0.0 vs. 20.0 vs. 11.1; (2) NA vs. 0.0 vs. 0.0 Acute otitis media:(1) 50.0 vs. 28.6 vs. 75.0; (2) 66.7 vs. 0.0 vs. 0.0 Acute bronchitis: (1) 23.7 vs. 20.0 vs. 39.2; (2) 22.2 vs. 25.0 vs. 10.0 Influenza: (1) 0.0 vs. 4.3 vs. 5.9; (2) NA vs. 0.0 vs. 0.0 * Adjustment for patient age, sex, education (not otherwise reported), and days with restrictions at baseline.	NR
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Briel, 2006 Switzerland Patient N = 837 (259 vs. 293 vs. 285) Provider N = 45 (15 vs. 15. vs. 15) Practice N = 45 (15 vs. 15. vs. 15)	NR	Full Intervention vs. Limited Intervention vs. Control Days with restricted activities, mean [SD]: 6.18 [3.94] vs. 6.81 [3.94] vs. 7.28 [4.09]; Adjusted* difference in mean days restricted (Full vs. Limited): -0.40; 95% CI, -1.07 to 0.27 Re-consultation within 14 days (%): 44.7 vs. 49.3 vs. 41.9; Adjusted* rate ratio (Full vs. Limited): 0.97; 95% CI, 0.78 to 1.21 Patients off work within 14 days (%): 53.4 vs. 47.2 vs. 58.1; Adjusted* OR (Full vs. Limited): OR=1.00; 95% CI, 0.63 to 1.57 Patients with satisfaction score of 70 out of 70 (%): 47.8 vs. 49.0 vs. 45.2 Adjusted* OR (Full vs. Limited): OR=1.00; 95% CI, 0.64 to 1.31 * Adjustment for patient age, sex, education (not otherwise reported), and days with restrictions at baseline.
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Briel, 2006 Switzerland Patient N = 837 (259 vs. 293 vs. 285) Provider N = 45 (15 vs. 15. vs. 15) Practice N = 45 (15 vs. 15. vs. 15)	Full Intervention vs. Limited Intervention vs. Control Patient enablement score (0-12), mean [SD]: 8.49 [1.98] vs. 8.15 [2.03] vs. 8.19 [1.90] Adjusted* difference in mean scores (Full vs. Limited): 0.35; 95% CI, -0.05 to 0.75 * Adjustment for patient age, sex, education (not otherwise reported), and days with restrictions at baseline.	NR	
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Brittain-Long, 2011 Sweden Patient N = 447 randomized; 406 available for analysis; 335 for secondary outcome Provider N = NR Practice N = NR	Age ≥ 18 years and a diagnosis of community acquired ARTI, defined as having a history of at least two of the following symptoms: coryza/nasal congestion/sneezing, sore throat/odynophagia, cough, pleuritic chest pain, shortness of breath or fever for which the physician found no other explanation, with a duration of less than 14 days	NR	Type: Clinical - POC: Multiviral Target: Provider Description: Patients were randomized to one of the following groups: (1) rapid result cohort or (2) delayed result cohort. Physicians treating patients in the rapid result cohort received results from the multiplex PCR analysis on the day following inclusion. Nasopharyngeal and throat swabs were collected on the day of inclusion (initial visit) and after 10 days (followup visit). Physicians treating patients in the delayed result cohort received results 8 to 12 days later. Multiplex PCR method targeted 13 viruses and 2 bacteria: parainfluenza virus types 1-3, influenza A and B, human metapneumovirus, respiratory syncytial virus, human rhinovirus, enterovirus, adenovirus, and human coronavirus types 229E, OC43, and NL63, along with bacterial Mycoplasma pneumoniae and Chlamydophila pneumoniae.
Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Brittain-Long, 2011 Sweden Patient N = 447 randomized; 406 available for analysis; 335 for secondary outcome Provider N = NR Practice N = NR	Rapid result vs. delayed result (control)	Type of RTI: ARTI Types of Signs and Symptoms: Coryza (83.3%), sore throat (76.4%), headache (73.4%), dry cough (64.5%), productive cough (56.2%), shortness of breath (55.2%), fever (53.0%), myalgia (51.0%), red eyes (40.4%), joint pain (39.9%), chest pain (22.9%), diarrhea (9.4%), vomiting (6.4%), rash (5.7%)	Mean age: 39 % female: 58.4% Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: Asthma (10.9%), COPD (1.7%), Allergies (7.0%), Diabetes (1.3%), Neoplastic disease (1.3%), Autoimmune disease (3.1%), Ischemic heart disease/angina (1.3%)
-Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Brittain-Long, 2011 Sweden Patient N = 447 randomized; 406 available for analysis; 335 for secondary outcome Provider N = NR Practice N = NR	Specialty: Mix Number of years in practice: NR Type of clinic: 12 outpatient clinics (eight primary health care centers and four departments of infectious disease) Geographical region: Sweden Population served: NR	Time of year: October 2006 to April 2009 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	NR
Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Brittain-Long, 2011 Sweden Patient N = 447 randomized; 406 available for analysis; 335 for secondary outcome Provider N = NR Practice N = NR	Rapid result vs. Delayed result Initial antibiotic treatment (n, %): 9 (4.5) vs. 25 (12.3), p=0.005 At initial visit: 7 (3.5) vs. 21 (10.3) After 24 to 48 hours: 2 (1.0) vs. 4 (2.0) Antibiotics prescribed at followup: 13.9 % vs. 17.2%, p=0.359 Antibiotics prescribed by detected pathogen (n, %) Patients with virus detected: 3 (3.3) vs. 11 (12.1), p=0.03 Patients with Mycoplasma pneumoniae detected: 2 (NR) vs. 2 (NR) Patients with Chlamydophila pneumoniae detected: 1 (NR) vs. NR	NR
Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Brittain-Long, 2011 Sweden Patient N = 447 randomized; 406 available for analysis; 335 for secondary outcome Provider N = NR Practice N = NR	NR	NR
Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Brittain-Long, 2011 Sweden Patient N = 447 randomized; 406 available for analysis; 335 for secondary outcome Provider N = NR Practice N = NR	NR	NR	
Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Patient N = 431 (Cals, 2009, 2011), 379 (Cals, 2013) Provider N = 40 Practice N = 20	Cals 2009 Patients eligible if they had a suspected lower LRTI with a cough lasting less than 4 weeks together with one focal and one systemic symptom Cals 2011 Patients aged 18 years or older with new episode of acute cough of up to 28 days and caused by LRTI as determined by GP	General practitioners (N=40) from 20 general practices	Type: Multifaceted - POC: C-reactive Protein Testing and Enhanced Communication Training Target: Providers Description: Three intervention groups: (1) CRP testing, (2) training in enhanced communication skills, and (3) interventions combined. Groups were combined for analysis in the following factors: Factor A (CRP compared with no test) and Factor B (training in enhanced communication skills compared with no training). CRP assessed with NycoCard II Reader with results available within 3 minutes. General practitioners underwent 30 minutes of training on how to use CRP results within the consultation. Communication skills intervention was built around 11 key tasks (e.g. exploring patients' fears and expectations, asking patients' opinion on antibiotics, and outlining the natural of cough in lower respiratory tract infection.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Patient N = 431 (Cals, 2009, 2011), 379 (Cals, 2013) Provider N = 40 Practice N = 20	Usual care (control)	Type of RTI: LRTI (nonspecific) Types of signs and symptoms: Shortness of breath (63.1%), wheezing (36.7%), chest pain (58.7%), abnormalities in auscultation (53.1%), fever (40.6%), perspiration (45.0%), headache (48.0%), myalgia (46.6%), generally feeling unwell (78.7%) Duration of signs and symptoms: 10.2 days (mean duration of cough)	Cals 2009 Mean age: 49.9 % female: 61.5 Ethnicity: NR SES: NR Education level: Lower education (36.2%); Secondary education (36.5%); Higher education (27.3%) Frailty: NR Comorbidities: COPD (7.1%); Asthma (9.0%); Diabetes mellitus (4.2%); Heart disease (4.6%) Prior RTIs: NR Prior use of antibiotics: NR Cals 2011 Mean Age: 50.0 % female: 61.5 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: COPD (7.2%); Asthma (9.0%); Diabetes Mellitus (4.2%)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Patient N = 431 (Cals, 2009, 2011), 379 (Cals, 2013) Provider N = 40 Practice N = 20	Specialty: General practice Number of years in practice (mean): 15.0 years Type of clinic: General practice Geographical region: the Netherlands Population served: NR	Cals 2009 Time of year: Patients recruited in the winter periods from September 2005 until March 2007 and were observed until July 2010 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	Dutch College of General Practitioners guidelines on acute cough

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Patient N = 431 (Cals, 2009, 2011), 379 (Cals, 2013) Provider N = 40 Practice N = 20	Cals 2009 Antibiotic prescribing, % intervention vs. % control; crude 95% Cl; p: CRP test: Index consultation: 30.8; 95% Cl, 21.8 to 39.8 vs. 52.9; 95% Cl, 43.0 to 62.8; p=0.02, ICC = 0.12 At days 1 to 28: 44.9; 95% Cl, 35.2 to 54.6 vs. 58.3; 95% Cl, 48.5 to 68.1, p <0.01, ICC = 0.12 Communication skills training: Index consultation: 27.4; 95%Cl, 25.6 to 36.6 vs. 53.5; 95%Cl, 43.8 to 63.2; p=0.01, ICC =0.12 At days 1 to 28: 37.8; 95%Cl, 28.1 to 47.5 vs. 63.0 95%Cl, 53.6 to 72.4; p<0.001, ICC = 0.12 Sensitivity Analysis: CRP test vs. Communication skills training vs. CRP test and communication skills training vs. usual care: 39 Antibiotic Prescribing at Index Consultation (% (crude 95% CI)): 39; 95%Cl, 25.6 to 52.6 vs. 33; 95%Cl, 19.5 to 47.1 vs. 23; 95%Cl,11.6 to 34.6 vs. 67; 95%Cl, 53.9 to 79.5 Cals 2011 Antibiotics at index consultation (no. (%)): CRP vs. Communication skills training vs. CRP and communication skills training vs. usual care: 43 (39.1) vs. 28 (33.3) vs. 27 (23.1) vs. 80 (66.7)	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Patient N = 431 (Cals, 2009, 2011), 379 (Cals, 2013) Provider N = 40 Practice N = 20	NR	Cals 2009 CRP test, % intervention vs. % control (crude 95% CI): Reconsultation within 28 days: 34.8; 95%CI, 28.3 to 41.3 vs. 30.4; 95%CI, 23.8 to 37.0; p=0.50, ICC = 0.01 Communications skills training, % intervention vs. % control (crude 95% CI): Reconsultation within 28 days: 27.9; 95%CI, 21.4 to 34.4 vs. 37.0; 95%CI, 30.4 to 43.6; p=0.14, ICC = 0.01 Patient Satisfaction, % at least very satisfied (crude 95% CI): CRP vs. no CRP: 76.8; 95%CI, 70.8 vs. 82.8 vs. 76.0; 95%CI, 69.6 to 82.4, p=0.53 Communication skill training vs. no communication skills training: 78.7; 95%CI, 72.5 to 84.9 vs. 74.4; 95%CI, 68.2 to 80.6, p=0.88 Cals 2011 CRP vs. communication skills training vs. CRP and communication skills training vs. usual care Days off of work, days (SD): 3.35 (4.54) vs. 3.37 (4.02) vs. 3.39 (4.08) vs. 3.37 (3.77) Average resource use per intervention group (physician visits): GP reconsultation: 0.40 vs. 0.18 vs. 0.27 vs. 0.37 GP out of hours office: 0.01 vs. 0.05 vs. 0.02 vs. 0.08 Hospital (outpatient or ED): 0.02 vs. 0.00 vs. 0.02 vs. 0.00

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Patient N = 431 (Cals, 2009, 2011), 379 (Cals, 2013) Provider N = 40 Practice N = 20	NR	Cals 2011 CRP vs. communication skills training vs. CRP and communication skills training vs. usual care Average resource use per intervention group (diagnostic testing): Chest x-ray: 0.05 vs. 0.05 vs. 0.09 vs. 0.07 Blood: 0.01 vs. 0.01 vs. 0.05 vs. 0.00 Other (spirometry, sputum): 0.02 vs. 0.00 vs. 0.02 vs. 0.02	Cals 2011 Primary outcome measures: health care cost. Cost-effectiveness of antibiotic prescribing at index consultation assessed by incremental cost-effectiveness ratios

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Patient Population Criteria	Provider Population Criteria	Intervention Strategy Type: (1) Educational/Behavioral (2) Communication (3) Clinical (4) System-Level (5) Multifaceted Target of Intervention (patient, provider, etc.) Intervention Description
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Continued.			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Continued.			Cals 2013 Mean age (SD): 49.9 (15.0) years % Female: 62.0 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: COPD (6.3%); Asthma (8.2%) Prior use of antibiotics: at index visit of trial (42.2%); during 28-day followup period (52.0%)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Continued.			

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Continued.	Cals 2013 % RTI episodes treated with antibiotics, Control vs. Intervention; 95% CI CRP test: 35.7; 95%CI, 29.5 to 42.0 vs. 30.7; 95%CI, 25.0 to 36.4; uncorrected difference -5.0, corrected difference -4.1; p=0.36 Communication Skills Training: 39.1; 95%CI, 33.1 to 45.1 vs. 26.3; 95%CI, 20.6 to 32.0; uncorrected difference -12.8, corrected difference -10.4; p=0.02	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Continued.		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Cals, 2009 Cals, 2011 Cals, 2013 The Netherlands Continued.			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Cals, 2010 The Netherlands Patient N = 258 Provider N = 32 Practice N = 11	Patients 18 years and older who consulted for the first time for current episode of LRTI or rhinosinusitis. For LRTI, had to be less than 4 weeks and have at least 1 symptom/focal point: shortness of breath; wheezing; chest pain; auscultation abnormalities. At least 1 systemic sign had to be present: fever; perspiring; headache; myalgia; general feeling unwell. For rhinosinusitis, patients made a first consultation for the current episode of rhinosinusitis (duration of less than 4 weeks) with at least 1 of the following symptoms: history of rhinorrhea; blocked nose. At least 1 of the following symptoms or signs had to be present: purulent rhinorrhea, unilateral facial pain, headache, teeth pain, pain when chewing, maxillary/frontal pain when bending over, or worsening of symptoms after initial improvement.	Family physicians working in 11 family practice center in the southeastern part of the Netherlands	Type: Clinical - POC: C-reactive Protein Target: Providers Description: For the intervention group (CRP assistance), CRP was measured by the practice nurse within the consultation and patient returned to the physician with the test result. The physician could use the CRP test result in addition to clinical assessment to decide on management (immediate, delayed, or no antibiotics).

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Cals, 2010 The Netherlands Patient N = 258 Provider N = 32 Practice N = 11	No CRP assistance (control). Physician had to decide on a management strategy (immediate, delayed, or no antibiotics) based on clinical assessment and finish the consultation (usual care). CRP was measured and recorded by practice nurse after the consultation. Practice nurses did not communicate the test result to either physician or patient until after the study.	Type of RTI: LRTI (41.5%) or rhinosinusitis (58.5%) Types of Symptoms: LRTI: shortness of breath (62.6%), wheezing (34.6%), chest pain (54.2%), auscultation abnormalities (43.0%), fever (48.6%), perspiring (46.7%), headache (37.4%), myalgia (47.7%), generally feeling unwell (76.6%); Rhinosinusitis: purulent rhinorrhea (54.3%), blocked nose (76.8%), unilateral facial pain (55.0%), headache (73.5%), dental pain (31.1%), pain chewing (14.6%), pain at bending over (63.6%) Duration of Signs and Symptoms: LRTI mean: 8.4 days Rhinosinusitis mean: 9.7 days When counting started for duration: NR	Mean Age: 44.3 % Female: 69.4 Ethnicity: NR SES: NR Educational level: lower education (24.5%); secondary education (43.0%); higher education (32.5%) Frailty: NR Comorbidities: COPD (3.1%); Asthma (7.4%); Allergic rhinitis (9.7%); diabetes mellitus (5.0%); heart disease (5.4%)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Cals, 2010 The Netherlands Patient N = 258 Provider N = 32 Practice N = 11	Specialty: General/family practice Type of clinic: Family practice Geographical region: Southeastern Netherlands Population served: NR	Time of year: November 2007 to April 2008 Patterns of disease activity: NR Locally tailored: NR System level characteristics: NR	Antibiotic treatment required for only community-acquired pneumonia and small subgroups of the LRTIs and URTIs

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Cals, 2010 The Netherlands Patient N = 258 Provider N = 32 Practice N = 11	CRP assisted vs. Control Antibiotic use after index consultation Overall: 43.4% vs. 56.6%, RR=0.77; 95% CI, 0.56 to 0.98 Rhinosinusitis: 45.2% vs. 60.3% LRTI: 41.1% vs. 51.0% Antibiotic use after 28-day followup Overall: 52.7% vs. 65.1%, RR=0.81; 95% CI, 0.62 to 0.99 Rhinosinusitis: 57.5% vs. 69.2% LRTI: 46.4% vs. 58.8% By CRP category 0-20 mg/L (n=140): 26.0% vs. 49.3% 21-50 mg/L (n=62): 56.5% vs. 59.0% 51-100 mg/L (n=37): 68.2% vs. 66.7% > 100 mg/L (n=19): 81.8% vs. 87.5% Antibiotics received at index consultation Immediate antibiotics: 39.5% vs. 40.3% No antibiotics: 43.4% vs. 37.2% Delayed antibiotics: 17.1% vs. 22.5%	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Cals, 2010 The Netherlands Patient N = 258 Provider N = 32 Practice N = 11	NR	CRP assisted vs. Control Reconsult: 25.6% vs. 17.8, p=0.13 Patient satisfaction (patient at least very satisfied): 76.3% vs. 63.2%, p=0.03 Clinical recovery in 7 days: 22.9% vs. 24.8%, p=0.73

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Cals, 2010 The Netherlands Patient N = 258 Provider N = 32 Practice N = 11	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Carling, 2009 Norway Patient N = 1760 Provider N = NR Practice N = NR	At least 18 years of age and filling in questionnaire for first time; not required to have an RTI at time of participation	NR	Type: Educational Target: Patients Description: Internet-based graphical displays of information about the effects of antibiotics on the symptoms of sore throat. Participants were randomized to one of four graphical displays for intervention: (1) face icons (happy/sad) displaying proportion of people who still have sore throat on day three with and without antibiotics (2) a bar graph displaying the same information, (3) a bar graph displaying the difference in average duration of symptoms, and (4) a bar graph displaying the proportion of people with sore throat symptoms at onset and on days three and seven. Patients randomized to graphic display were given the same textual information on the pros and cons of antibiotic use. Participants were asked to indicate whether or not they would go to the doctor for antibiotics (first decision). Next, all participants were shown all displays in block-randomized sequence and asked to decide if they would go to the doctor for antibiotics (second decision)
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Carling, 2009 Norway Patient N = 1760 Provider N = NR Practice N = NR	No information (control)	NR	Age: 31.7% ages 30-39 y % female: 69.4 Ethnicity: NR SES: NR Educational level: 72.6% university educated, 24.0% high school educated, 3.5% elementary educated Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Carling, 2009 Norway Patient N = 1760 Provider N = NR Practice N = NR	NR	Time of year: September - October 2004 Patterns of disease activity: NR Locally tailored: Yes, displays in Norwegian; study publicized on popular nationally televised Norwegian weekly health program System-level characteristics: Internet-based intervention	NR
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Carling, 2009 Norway Patient N = 1760 Provider N = NR Practice N = NR	NR	NR
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Carling, 2009 Norway Patient N = 1760 Provider N = NR Practice N = NR	NR	NR
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Carling, 2009 Norway Patient N = 1760 Provider N = NR Practice N = NR	Odds of Visiting the Doctor by Display Type: OR; 95% CI; p-value Face icons % symptoms at day 3 vs. bar graph % symptoms at day 3: OR=1.08; 95 % CI, 0.78 to 1.50; p=0.65 Bar graph duration of symptoms vs. bar graph % symptoms at day 3: OR=0.39; 95% CI, 0.27 to 0.57; p<0.001 Bar graph % symptoms at days 3 and 7 vs. bar graph % symptoms at day 3: OR=0.74; 95% CI, 0.52 to 1.05; p=0.10 Odds ratios for deciding to go to the doctor on first decision for each group compared with fully informed second decision for other four groups: OR; 95% CI Face icons, % symptoms at day 3: OR=2.20; 95% CI, 1.68 to 2.88 Bar graph, % symptoms at day 3: OR=2.08; 95% CI, 1.59 to 2.73 Bar graph, duration of symptoms: OR=0.72; 95% CI, 0.53 to 0.98 Bar graph, % symptoms at days 3 and 7: OR=1.50; 95% CI, 1.11 to 2.01 No information: OR=0.93; 95% CI, 0.70 to 1.24	NR	
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Chazan, 2007 Israel Patient N = 168,644 Provider N = 200 Practice N = NR	NR	Doctors (general practitioners, pediatricians, and family physicians), nurses, and pharmacists working in clinics and pharmacies belonging to Clalit Health Services	Type: Educational Target: Providers Description: Continuous intervention consisting of monthly interactive teaching sessions consisting of a 'group education meeting' focusing on practical diagnostic tools directed at the decision 'to treat or not treat' with antibiotics, providers were given therapeutic recommendations for common infectious diseases distinguishing between viral and bacterial infections
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Chazan, 2007 Israel Patient N = 168,644 Provider N = 200 Practice N = NR	Seasonal intervention consisting of a massive educational campaign prior to two consecutive winters promoting judicious use of antibiotics to treat RTIs, consisted of a 2 hour interactive meeting, informative reminders given to providers, educational leaflets given to providers for their patients	NR	Mean Age: 32 y % female: 49.9 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Chazan, 2007 Israel Patient N = 168,644 Provider N = 200 Practice N = NR	Specialty: Mix Number of years in practice: NR Type of clinic: 16 largest community clinics in Clalit Health Services HMO Geographical region: Israel Population served: provides services to 70% of population in north of the country, including 442,758 Jews, Christian Arabs, and Moslems living in urban and rural areas	Time of year: October 2000 - April 2003 Patterns of disease activity: NR Locally tailored: Yes System level characteristics: Clinics were part of Clalit Health Services HMO	NR
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Chazan, 2007 Israel Patient N = 168,644 Provider N = 200 Practice N = NR	Total Antibiotic Use November 2002-2003 vs. Baseline (November 1999-2000) (reported in defined daily dose/1000 patients/day) Seasonal intervention group: 23.2 vs. 27.8 Continuous Intervention group: 22.9 vs. 28.7 (p for difference between groups <0.0001) % decrease in antibiotic use, continuous vs. seasonal intervention: 20.0% vs. 16.5% (p<0.0001)	NR
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)		
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Chazan, 2007 Israel Patient N = 168,644 Provider N = 200 Practice N = NR	NR	NR
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)		
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Chazan, 2007 Israel Patient N = 168,644 Provider N = 200 Practice N = NR	NR	NR	
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Coenen, 2004 Belgium Patient N = 1,503 Provider N = 85 Practice N = NR	Adult patients with acute cough, ages 18-65, immunocompetent, with new or worsening cough, present for <30 days as one of the most important complaints and as the reason for the first encounter with the practice	Flemish GPs	Type: Educational Target: Providers Clinical practice guideline for management of acute cough in general practice, educational outreach visit and postal message on key messages
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)			
Croft, 2007 (Please refer to Andrews, 2012 systematic review)			
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Coenen, 2004 Belgium Patient N = 1,503 Provider N = 85 Practice N = NR	Leaflets from a public campaign	Patient characteristics: Type of RTI: acute cough Types of Signs and Symptoms: cough, sputum, fever, runny nose, headache, muscle ache, sore throat, wheezing, shortness of breath, chest pain, loss of appetite, limited activity Duration of Signs and Symptoms: predicted mean duration of cough When counting started for duration: NR	Patient characteristics: table 2 Mean Age: 40.2-41.9 % female: 57-60% Ethnicity: NA SES: NR Educational level: NR Frailty :NR Comorbidities: asthma (7-14%), COPD (7-9%), Heart failure (0-2%), CVD (0-2%) Prior RTIs: NR Prior use of antibiotics: NR
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)			
Croft, 2007 (Please refer to Andrews, 2012 systematic review)			
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Coenen, 2004 Belgium Patient N = 1,503 Provider N = 85 Practice N = NR	Specialty: GP Number of years in practice: NR Type of clinic: NR Geographical region: Belgium Population served: general adult population	Time of year: December 2000-January 2001 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	Recommended antibiotic (narrow spectrum i.e., Amoxicillin or doxycycline) used if antibiotics are prescribed; no definition for when appropriate to not use antibiotics
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)			
Croft, 2007 (Please refer to Andrews, 2012 systematic review)			
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Coenen, 2004 Belgium Patient N = 1,503 Provider N = 85 Practice N = NR	Intervention vs. controls, # (%) Prescriptions Pre-intervention: 318 (87) vs. 388 (87) Post-intervention: 285 (98) vs. 377 (94) Rate of use and % difference in change of use of antibiotics Use of antibiotics Pre-intervention 43 vs. 37.8 Post-intervention 27.4 vs. 28.7 % change -15.6 vs. -9.1 % difference -6.5 OR/ICC: OR=0.74; 95% CI, 0.51 to 1.08/0.18 OR, adjusted/ICC: OR=0.56; 95% CI, 0.36 to 0.87/0.22	NR
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)		
Croft, 2007 (Please refer to Andrews, 2012 systematic review)		
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Coenen, 2004 Belgium Patient N = 1,503 Provider N = 85 Practice N = NR	Interventions vs. controls (%) Hospitalization: Pre-intervention: 0 vs. 1	Interventions vs. controls (%) Time to symptom resolution: Reported to be similar with no significant differences. Post-intervention: 2 vs. 0 Reconsultation: Pre-intervention: 57 (23%) vs. 55 (20%) Post-intervention: 40 (19%) vs. 61 (22%)
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)		
Croft, 2007 (Please refer to Andrews, 2012 systematic review)		
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Coenen, 2004 Belgium Patient N = 1,503 Provider N = 85 Practice N = NR	NR	Diagnostic resource use: Intervention vs controls, # (%) Radiograph Pre-intervention: 7 (2) vs. 23 (5) Post-intervention: 3 (1) vs. 11 (3) Sputum analysis Pre-intervention: 0 vs. 12 (3) Post-intervention: 1 (0) vs. 4 (1) serology Pre-intervention: 1 (0) vs. 7 (2) Post-intervention: 2 (1) vs. 9 (2) Sustainability: No difference in change in 1st month and last 2 months post-intervention.	
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)			
Croft, 2007 (Please refer to Andrews, 2012 systematic review)			
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Diederichsen, 2000 Denmark Patient N = 812 Provider N = NR Practice N = 35	Patients of all ages who consulted their GP during normal working hours because of RTIs, and who belonged to the National Health Insurance Group 1	NR	Type: Clinical - POC: C-reactive Protein Target: Provider and Patients Description: Intervention group used CRP rapid test and clinical assessment. CRP analysis carried out during consultation by means of NycoCard: CRP (sensitivity and specificity NR). GPs were informed that normal CRP values are < 10 mg/L and CRP values < 50 mg/L were seldom the result of infection. No strict guidelines for the use of antibiotics in relation to the CRP value were given. Patient questionnaire administered at consultation.
Doan, 2009 (Please refer to Doan, 2014 systematic review)			
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)			
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)			
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)			
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Diederichsen, 2000 Denmark Patient N = 812 Provider N = NR Practice N = 35	Clinical assessment only (control)	Type of RTI: Respiratory infections (nonspecific) Types of Symptoms: Fever (51%), cough (81%), pain (49), well-being affected (32%) Duration of Signs and Symptoms: < 1 day (3%), 1-3 days (26%), 4-7 days (37%), >7 days (38%) When counting started for duration: NR	Mean Age: 37 years % Female: 57 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR
Doan, 2009 (Please refer to Doan, 2014 systematic review)			
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)			
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)			
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)			
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Diederichsen, 2000 Denmark Patient N = 812 Provider N = NR Practice N = 35	Specialty: General practice Number of years in practice: NR Type of clinic: General practice Geographical region: County of Funen, Denmark Population served: NR	Time of year: January 2, 1997 to April 30, 1997 Patterns of disease activity: NR Locally tailored: NR System level characteristics: Patients in National health Insurance Group 1	NR
Doan, 2009 (Please refer to Doan, 2014 systematic review)			
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)			
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)			
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)			
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Diederichsen, 2000 Denmark Patient N = 812 Provider N = NR Practice N = 35	CRP Group vs. Control % Antibiotic Prescription %; 95% CI; OR; 95% CI: 43%; 95%CI, 40% to 47% vs. 46%; 95%CI, 43% to 50%; OR=0.9; 95% CI, 0.70 to 1.20 Factors influencing GP's decision to prescribe antibiotics: CRP value (per unit increase (mg/L)): 1.09 (1.06 to 1.12) vs. NR	NR
Doan, 2009 (Please refer to Doan, 2014 systematic review)		
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)		
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)		
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)		
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Diederichsen, 2000 Denmark Patient N = 812 Provider N = NR Practice N = 35	NR	CRP Group vs. Control Increased or unchanged morbidity after 1 week %; 95% CI; OR; 95% CI; p: 12%; 95%CI, 10% to 15% vs. 8%; 95%CI, 6% to 10%; OR=1.6; 95% CI, 1.0 to 2.6; p=0.05
Doan, 2009 (Please refer to Doan, 2014 systematic review)		
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)		
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)		
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)		
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Diederichsen, 2000 Denmark Patient N = 812 Provider N = NR Practice N = 35	NR	NR	
Doan, 2009 (Please refer to Doan, 2014 systematic review)			
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)			
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)			
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)			
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Finkelstein, 2008 United States Patient N = 233,135 person-years of observation Provider N = NR Practice N = NR	Children aged 3 to < 72 months, who resided in study communities (16 non-overlapping Massachusetts communities), and were insured by a participating commercial health plan or Medicaid	Pediatricians and family physicians in intervention communities	Type: Educational Target: Providers and Parents Description: Three year intervention involving the implementation of a physician behavior-change strategy that included guideline dissemination, small-group education, frequent updates and educational materials, and prescribing feedback. Educational materials for parents included trifold brochure entitled "Kids and Antibiotics" and an information sheet on appropriate antibiotic use to be used during well-child visits. Prescription pads adapted from CDC-sponsored campaigns were provided to physicians. A variety of stickers, lapel pins, otoscope insufflators, and additional materials with REACH Mass logo were also distributed. Newsletters, interactive website, posters, and counter-top displays were targeted at parents.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Finkelstein, 2008 United States Patient N = 233,135 person-years of observation Provider N = NR Practice N = NR	Control communities (those not receiving intervention)	Type of RTI: NR Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Mean Age % female: NR Ethnicity: Nonwhite (10%) SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Finkelstein, 2008 United States Patient N = 233,135 person-years of observation Provider N = NR Practice N = NR	Specialty: Pediatrics and family practice Number of years in practice: NR Type of clinic: NR Geographical region: Massachusetts Population served: Children	Time of year: October to March from 2000 to 2003 Patterns of disease activity: Intervention conducted during 3 consecutive cold and flu seasons Locally tailored: Yes System-level characteristics: 16 Massachusetts communities in collaboration with Massachusetts Department of Public Health and four large health insurers (including Medicaid)	CDC guidelines for judicious antibiotic prescribing for use in Massachusetts adapted by panel of local content experts and representatives of Massachusetts Department of Public Health

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Finkelstein, 2008 United States Patient N = 233,135 person-years of observation Provider N = NR Practice N = NR	Control vs. Intervention Overall Antibiotic Use Rates in Year 1 of Study by Age Group (unadjusted rate, adjusted % change): 3 to <24 months: 2.8, -20.7 vs. 2.9, -21.2; intervention effect -0.5 ; p=0.69 24 to <48 months: 1.7, -10.3 vs. 1.7, -14.5; intervention impact -4.2; p<0.01 48 to <72 months: 1.4, -2.5 vs. 1.4, -9.3; intervention impact -6.7; p<0.0001	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Finkelstein, 2008 United States Patient N = 233,135 person-years of observation Provider N = NR Practice N = NR	NR	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Finkelstein, 2008 United States Patient N = 233,135 person-years of observation Provider N = NR Practice N = NR	NR	NR	*unadjusted rates were calculated as the sum of all antibiotic dispensing divided by the sum of the person-years observed. Adjusted percentage change over all 3 intervention years (study years 3-5, September 1, 2000, to August 31, 2003) from generalized linear mixed models, accounting for clustering by community, baseline prescribing rate, differences in baseline trend (year 1 to 2), secular trend during the intervention period, and gender. Insurance type (Medicaid versus commercial) was included as a covariate in the model of overall effect

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Forrest, 2013 United States Patient N = 139,305 patient visits for otitis media Provider N = 24 practices	Children with otitis media	PCP practices.	Type: System-level Target: Providers Description: Randomization at level of clinical practice within pediatric research Consortium (a practice based research network). Used a locally adapted electronic record-based patient-specific clinical decision support tool with or without monthly feedback on performance to clinicians
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)			
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Forrest, 2013 United States Patient N = 139,305 patient visits for otitis media Provider N = 24 practices	Usual care (n=4 practices) versus CDS with feedback (n=8) versus CDS only (n=4)	Children with acute OM included (includes both AOM and OME---otitis media with effusion). Excluded visits for Otitis externa and resolved OM	NR
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)			
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Forrest, 2013 United States Patient N = 139,305 patient visits for otitis media Provider N = 24 practices	Specialty: Pediatrician/primary care Number of years in practice: Variable Type of clinic: Primary care Geographical region: Pennsylvania Population served: Pediatrics	NR	Defined as per AOM guidelines that were provided to clinicians for each patient OM visit
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)			
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Forrest, 2013 United States Patient N = 139,305 patient visits for otitis media Provider N = 24 practices	One of several metrics measured in study with regard to adherence to AOM guidelines. For our purposes: "watchful waiting" is primary outcome---i.e. not using antibiotics according to guidelines. Major problem with study is that for only 17% of eligible visits was the CDS tool even used by PCPs. For results---there was no difference between any group with regard to comparison to baseline period or each other for adherence to watchful waiting guidelines. For AOM---percent difference in those adhering after intervention (by visit) CDS (0.1%) versus -0.7% (non-CDS), and for OME -3.2% CDS versus -1.3% (non-CDS). Very unclear if they measured this difference only among visits where the CDR was used? assume they used ITT and disregarded this and this likely explains why there was no difference, because no one used the CDR! at baseline, clinicians only used watchful waiting for 6% of visits, and this did not change after study start	NR
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)		
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Forrest, 2013 United States Patient N = 139,305 patient visits for otitis media Provider N = 24 practices	NR	NR
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)		
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Forrest, 2013 United States Patient N = 139,305 patient visits for otitis media Provider N = 24 practices	NR	NR	
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)			
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Gerber, 2013 United States Patient N = 185,212 unique patients (1,291,824 office visits) Provider N = 162 Practice N = 18	Children with chronic medical conditions, antibiotic allergies, and prior antibiotic use were excluded	Primary care pediatricians working in a hospital-affiliated network of 29 pediatric primary care sites	Type: Educational Target: Providers Description: One 1-hour on-site clinician education session (June 2010) followed by 1 year of personalized, quarterly audit and feedback of prescribing for bacterial and viral ARTIs
Gjelstad, 2013 Norway Patient N = NR Provider N = 79,382 GPs Practice N = NR	Patients with acute respiratory tract infections diagnoses	Norwegian GPs attending a continuing medical education group	Type: Multifaceted Target: Providers Description: Educational (aimed at providers): national clinical practice guidelines for appropriate use of antibiotics for acute RTI, supplemented with research evidence; encouraged to use delayed prescribing; and System level: individual reports based on captured data to each GP showing RX rates and distribution of different antibiotics for various acute RI diagnoses

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Gerber, 2013 United States Patient N = 185,212 unique patients (1,291,824 office visits) Provider N = 162 Practice N = 18	No education or prescribing feedback (usual practice)	Type of RTI: bacterial ARTI (acute sinusitis (2.9%), streptococcal pharyngitis (2.6%), and pneumonia(0.7%)) and viral ARTI Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Mean Age: 5 years % female: 49% Ethnicity: Black (11%) SES: Medicaid (15%) Educational level: NR Frailty: NR Comorbidities: Allergy (13.3%) Prior RTIs: NR Prior use of antibiotics: 26.8%
Gjelstad, 2013 Norway Patient N = NR Provider N = 79,382 GPs Practice N = NR	Antibiotic intervention, group visits, peer academic detailer, individual prescription reports and CME about appropriate antibiotic prescribing vs. above intervention about *general prescribing in patients >70* (excluding antibiotics)	Type of RTI: upper respiratory tract infections and respiratory symptoms, ear infections, acute tonsillitis, acute sinusitis, acute bronchitis, pneumonia Types of Signs and Symptoms: upper respiratory symptoms Duration of Signs and Symptoms: NR When counting started for duration: NR	Mean Age: 19-44 % female: 57% Ethnicity: NA SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Gerber, 2013 United States Patient N = 185,212 unique patients (1,291,824 office visits) Provider N = 162 Practice N = 18	Specialty: Pediatrics Number of years in practice: NR Type of clinic: Pediatric primary care Geographical region: Pennsylvania and New Jersey Population served: Children from diverse racial and socioeconomic backgrounds in urban, suburban, and rural settings	Time of year: October 2008 to June 2011 (total study period); June 2010 to June 2011 (intervention period) Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Hospital-affiliated network	American Academy of Pediatrics (AAP) recommendations of penicillin or amoxicillin as first-line agents for acute sinusitis, streptococcal pharyngitis, and pneumonia
Gjelstad, 2013 Norway Patient N = NR Provider N = 79,382 GPs Practice N = NR	Specialty: General practice Number of years in practice: NR Type of clinic: city practice, group practice, specialist practice Geographical region: Netherlands Population served: general population	Time of year: December 2005 to March 2006; April and May 2006 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: National Health Service	Based on Norwegian guidelines of appropriate antibiotic use

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Gerber, 2013 United States Patient N = 185,212 unique patients (1,291,824 office visits) Provider N = 162 Practice N = 18	Rate of broad spectrum antibiotic prescribing during 1 year intervention, intervention vs. control: 26.8% to 14.3%, absolute difference 12.5% vs. 28.4% to 22.6%, absolute difference 5.8%; Difference of differences (DOD), 6.7%; p=0.01 Rate of antibiotic prescribing for bacterial ARTI during 1 year intervention, intervention vs. control: Acute sinusitis: 38.9% to 18.8% vs. 40.0% to 33.9%, Difference of differences (DOD) 14.0%; p=0.12 Streptococcal pharyngitis: 4.4% to 3.4% vs. 5.6 to 3.5%, Difference of differences (DOD) -1.1%; p=0.82 Rate of antibiotic prescribing for viral ARTI during 1 year intervention, intervention vs. control: 7.9% to 7.7% vs. 6.4% to 4.5%; Difference of differences (DOD) -1.7%; p=0.93	NR
Gjelstad, 2013 Norway Patient N = NR Provider N = 79,382 GPs Practice N = NR	Changes in rates of antibiotic prescriptions: mean; 95% CI proportion of ARTI episodes with antibiotic prescription Before intervention: 31.7; 95%CI, 29.4-34 vs. 32.7; 95%CI, 30.2 to 35.2 After intervention: 30.4; 95%CI, 27.9 to 32.8 vs. 34.2; 95%CI, 31.5 to 37 Change: -1.29; 95%CI, -2.43 to -0.16; -4.1% (relative) vs. 1.49; 95%CI, 0.58 to 2.4; 4.6% (relative)	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Gerber, 2013 United States Patient N = 185,212 unique patients (1,291,824 office visits) Provider N = 162 Practice N = 18	NR	NR
Gjelstad, 2013 Norway Patient N = NR Provider N = 79,382 GPs Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Gerber, 2013 United States Patient N = 185,212 unique patients (1,291,824 office visits) Provider N = 162 Practice N = 18	NR	NR	
Gjelstad, 2013 Norway Patient N = NR Provider N = 79,382 GPs Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Gonzales, 2011 United States Patient N = 139 enrolled (131 completed ED visit) Provider N = NR Practice N = NR	Patients ≥ 18 years; new cough present ≤ 21 days; at least one other ARI symptom (fever, sore throat, night sweats, body aches, nasal or chest congestion, shortness of breath); and availability for telephone followup interview in 2-4 weeks	NR	Type: Clinical - POC: C-reactive Protein Target: Provider Description: All participants had a management algorithm with recommendations on chest X-ray study ordering and antibiotic treatment of adults with acute cough illness placed in their medical chart. Intervention group included use of bedside fingerstick, whole blood specimen CRP test performed by study nurse with results placed in chart before being seen by clinician. Recommendation for further diagnostic testing or antibiotic treatment based on clinical algorithm provided to the control group plus CRP level categorized as normal (<10 mg/L), indeterminate (10-99 mg/L), or high (>100 mg/L)
Gonzales, 2013 United States Patient N = NA Provider N = NR Practice N = 33 PCP sites	Uncomplicated acute bronchitis age>12 years old to 64 years old, October 1-March 31st of each year	Geisinger Health System	Type: System-level Target: Providers and patients Description: System-level printed decision support (PDS) versus computer-assisted decision-support (CDS) versus control (no support) for ACI along with clinical education and feedback.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Gonzales, 2011 United States Patient N = 139 enrolled (131 completed ED visit) Provider N = NR Practice N = NR	No CRP testing (control); recommendations for chest X-ray study or antibiotic treatment based on clinical algorithm for predicting pneumonia in adults with acute cough illness	Type of RTI: Bronchitis (37.4%), otitis media (2.3%), pharyngitis (3.1%), sinusitis (6.1%), URI (32.8%) Types of Symptoms: NR Duration of Signs and Symptoms (mean): 5.15 days When counting started for duration: NR	Mean Age: NR; 18-44 (61%), 45-64 (35.8%), ≥ 65 (3%) % Female: 65.6% Ethnicity: Black (45.8%), White (25.2%), Hispanic (0%), Other (3.8%), unable to determine (25.2%) SES: NR Educational level: NR Frailty: NR Comorbidities: COPD (5.3%), Asthma (22.9%), Diabetes (11.5%) Prior RTIs: 2.3% (in previous 6 weeks)
Gonzales, 2013 United States Patient N = NA Provider N = NR Practice N = 33 PCP sites	Time-period before intervention (3 winter periods before)	Type of RTI: acute bronchitis (uncomplicated and without comorbidities) Types of Signs and Symptoms: ICD-9 code based. Patient with 466.0 and 490 without prior visit for these codes in prior 30 days. Of these patients, record reviewed to see which were "uncomplicated". Duration of Signs and Symptoms: NR When counting started for duration: NR	Age: 13-64 y % female: 56-63% female Ethnicity: 96-96% white, SES: NR Educational level: NR Frailty: NR Comorbidities Prior RTIs: NR Prior use of antibiotics: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Gonzales, 2011 United States Patient N = 139 enrolled (131 completed ED visit) Provider N = NR Practice N = NR	Specialty: NR Number of years in practice: NR Type of clinic: ED Geographical region: Urban setting, Midwest US Population served: NR	Time of year: November 2005 to March 2006 Patterns of disease activity: NR Locally tailored: NR System level characteristics: 1 of 8 control sites in previous 2 years as part of IMPAACT study	Recommendations for antibiotic treatment guided by CRP level categories
Gonzales, 2013 United States Patient N = NA Provider N = NR Practice N = 33 PCP sites	Provider characteristics: practices stratified by size and then randomized. Specialty: primary care Number of years in practice: NR Type of clinic: primary care Geographical region: Penn Population served: Geisinger	Used winter months only. Three year baseline prior to study compared with intervention year (same winter months).	Bronchitis in age group 13-64 years without presence of comorbidities and without antibiotic "responsive" secondary conditions including pharyngitis, sinusitis, otitis media, and pneumonia

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Gonzales, 2011 United States Patient N = 139 enrolled (131 completed ED visit) Provider N = NR Practice N = NR	CRP Group vs. Control Antibiotic treatment %; 95% CI; p: 37%; 95%CI, 26% to 48% vs. 31%; 95%CI, 19% to 43%; p=0.46	NR
Gonzales, 2013 United States Patient N = NA Provider N = NR Practice N = 33 PCP sites	Control: antibiotic use pre-intervention 72.5% to 74.3% post-intervention PDS: antibiotic use pre-intervention 80% to 68.3% post-intervention CDS: antibiotic use pre-intervention 74% to 60.7% post-intervention	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Gonzales, 2011 United States Patient N = 139 enrolled (131 completed ED visit) Provider N = NR Practice N = NR	CRP Group vs. Control Hospitalizations %; 95% CI; p: 6%; 95% CI, 2% to 16%) vs. 3%; 95% CI, 0.4%-12%, p=0.68	CRP Group vs. Control Return visits %; 95% CI; p: 40%; 95% CI, 28% to 52% vs. 33%; 95% CI, 21% to 45%), p=0.46
Gonzales, 2013 United States Patient N = NA Provider N = NR Practice N = 33 PCP sites	Measured patients who returned for second visit within 30 days later and diagnosed with pneumonia 0.5%-1.5% across the three groups during the intervention period.	"emergency dept. visits and hospital admission [within 30 days] were rare across all sites and periods" raw data reported in Table 1 and 0-0.1% between groups and periods.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Gonzales, 2011 United States Patient N = 139 enrolled (131 completed ED visit) Provider N = NR Practice N = NR	NR	NR	
Gonzales, 2013 United States Patient N = NA Provider N = NR Practice N = 33 PCP sites	NR	see KQ3	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Huang, 2007 United States Patient N = 1071 (2000 survey), 2071 (2003 survey) Provider N = NR Practice N = NR	Children < 6 years of age insured by 4 collaborating health plans: Harvard Pilgrim Health Care, Blue Cross Blue Shield of Massachusetts, Tufts Health Plan, and Mass Health (Massachusetts Medicaid program)	Local pediatric providers, pharmacies, and child care centers	Type: Educational Target: Parents of patients Description: Community intervention on parental misconceptions likely contributing to pediatric antibiotic overprescribing. Parents were mailed educational newsletters and were exposed to educational materials (e.g. stickers, posters, pamphlets, and fact sheets) during visits to local pediatric providers, pharmacies, and child care centers
Iyer, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Huang, 2007 United States Patient N = 1071 (2000 survey), 2071 (2003 survey) Provider N = NR Practice N = NR	No educational materials/no intervention (control)	NR	2000 Survey Population: Age: 55.5% 31-40 y % female: 90.5 (mother) Ethnicity: 88% White, 1% Black, 3% Hispanic, 7.5% Other SES: 69% employed Educational level: 3.5% less than high school, 43% college graduate, 53.5% high school graduate, some college Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR 2003 Survey Population: Age: 63% ages 31 - 40 y % female: 91.5 (mother) Ethnicity: 85% white, 3% black, 3% Hispanic, 9% other SES: 63% employed Educational level: 3% less than high school, 37% college graduate, 59.5% high school graduate, some college Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Iyer, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Huang, 2007 United States Patient N = 1071 (2000 survey), 2071 (2003 survey) Provider N = NR Practice N = NR	Specialty: Mix Number of years in practice: NR Type of clinic: local pediatric providers, pharmacies, and child care centers Geographical region: Massachusetts Population served: NR	Time of year: September 2000 - March 2003 Patterns of disease activity: Intervention occurred through 3 successive cold and flu seasons Locally tailored: Yes System level characteristics: Insured by 4 collaborating health plans, Harvard Pilgrim Health Care, Blue Cross Blue Shield of Massachusetts, Tufts Health Plan, and Mass Health (the Massachusetts Medicaid program).	NR
Iyer, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Huang, 2007 United States Patient N = 1071 (2000 survey), 2071 (2003 survey) Provider N = NR Practice N = NR	NR	NR
Iyer, 2006 (Please refer to Doan, 2014 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Huang, 2007 United States Patient N = 1071 (2000 survey), 2071 (2003 survey) Provider N = NR Practice N = NR	NR	NR
Iyer, 2006 (Please refer to Doan, 2014 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Huang, 2007 United States Patient N = 1071 (2000 survey), 2071 (2003 survey) Provider N = NR Practice N = NR	Proportion of Total Cohort with ≥ 7 of 10 Knowledge Questions Correct, % change from 2000 to 2003 surveys, p-value Intervention group: 12, p<0.05 Control group: 7, p< 0.05 Crude OR*: OR=1.2; 95% CI, 0.9 to 1.6 *Controlling only for survey year and community intervention/control status Intervention Effect** on Parental Knowledge of Antibiotics in Total Cohort, OR: OR=1.2; 95% CI, 0.8 to 1.7 **Intervention effect was measured as an interaction term between intervention and control status and time	NR	
Iyer, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Légaré, 2010 Quebec, Canada Patient N = 459 (15 per clinician) Provider N = 33 Practice N = 4 (2 vs. 2)	Inclusion: Seen by family physician (FP) for ARI during walk-in clinic hours; No age restriction; Able to read, understand and write in French. Exclusion: Condition requiring emergency care	Include: Family Medicine Group (FMG) in Quebec City area; Family practitioner; Plan to remain in practice for duration of the trial. Exclude: Previously participated in an implementation trial of shared decision making (SDM)	Type: (1) Educational/Behavioral and (2) Communication Target: Providers Description: Professional development program with 3 components: (1) Interactive workshops (n = 3) and related material to address: (a) probability of bacterial vs. viral URI, (b) scientific evidence of benefit/risk of various treatment options, (c) risk communication techniques, and (d) strategies for fostering patient participation in decisionmaking. Workshops included videos of simulated patient-FP consultations, facilitated exercises, decision support tools for clinical use, and educational materials. (2) Two types of reminders mailed to participants between workshops to: emphasize use of decision support tools in clinic, SDM behaviors, and new studies relevant to use of antibiotics for ARIs. (3) Research team informed FPs of level of agreement between their scores on the decisional conflict scale (DCS) and the DCS scores of their patients

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Légaré, 2010 Quebec, Canada Patient N = 459 (15 per clinician) Provider N = 33 Practice N = 4 (2 vs. 2)	Randomized (at FMG level) control group clinicians and patients. Study was a parallel clustered RCT, in which the control group received delayed intervention, and both groups were also compared with themselves at two time points	Experimental group (n = 245) vs. Control group (n = 214) (Three subgroups each) Type of RTI: NR Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR Time T0 (n = 169, 92 vs. 77): Preferred role in decisionmaking, % (n/N): Patient decides: 4% (4/92) vs. 4% (3/73); Patient decides, considering physician's opinion: 32% (29/92) vs. 33% (24/73); Both parties decide: 34% (31/92) vs. 19% (14/73); Physician decides, considering patient's opinion: 17% (16/92) vs. 33% (24/73); Physician decides: 13% (12/92) vs. 11% (8/73) Time T1 (n = 151, 81 vs. 70): Preferred role in decisionmaking, % (n/N): Patient decides: 5% (4/81) vs. 7% (5/70); Patient decides, considering physician's opinion: 43% (35/81) vs. 36% (25/70); Both parties decide: 20% (16/81) vs. 23% (16/70); Physician decides, considering patient's opinion: 23% (19/81) vs. 19% (13/70); Physician decides: 9% (7/81) vs. 16% (11/70) Time T2 (n = 139, 72 vs. 67): Preferred role in decisionmaking, % (n/N): Patient decides: 7% (5/72) vs. 3% (2/65); Patient decides, considering physician's opinion: 32% (23/72) vs. 26% (17/65); Both parties decide: 29% (21/72) vs. 18% (12/65); Physician decides, considering patient's opinion: 19% (14/72) vs. 32% (21/65); Physician decides: 13% (9/72) vs. 20% (13/65)	Experimental group (n = 245) vs. Control group (n = 214) (Three subgroups each) Time T0 (n = 169, 92 vs. 77): Adults: 60% (55/92) vs.79% (61/77) Age, years (adults), mean ± SD: 37 ± 12 vs. 41 ± 13 Age, years (children), mean ± SD: 4 ± 3 vs. 7 ± 5 Female: 67% (62/92) vs. 75% (57/77) SES (income ≥ Canadian $ 45,000/yr): 55% (51/92) vs. 54% (38/77) SES (currently working): 68% (63/92) vs.79% (61/77) SES (with public drug insurance): 29% (27/92) vs. 22% (17/77) Educational level (college degree): 55% (51/92) vs. 58% (44/77) Time T1 (n = 151, 81 vs. 70): Adults: 67% (54/81) vs.66% (46/70) Age, years (adults), mean ± SD: 36 ± 13 vs. 38 ± 12 Age, years (children), mean ± SD: 5 ± 4 vs. 5 ± 4 Female: 70% (57/81) vs.68% (47/70) SES (income ≥ Canadian $ 45,000/yr): 56% (43/81) vs.63% (42/70) SES (currently working): 72% (58/81) vs.83% (57/70) SES (with public drug insurance): 40% (32/81) vs.30% (21/70)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Légaré, 2010 Quebec, Canada Patient N = 459 (15 per clinician) Provider N = 33 Practice N = 4 (2 vs. 2)	Intervention vs. Control Specialty: All Family Practice Number of years in practice, mean ± SD: 22 ± 9 vs. 21 ± 10 Type of clinic: All FMGs affiliated with the Ministère de la Santé et des Services sociaux of Quebec Geographical region: All Quebec City Population served: All General population registered for services Preferred role in decisionmaking, % (n/N): Patient decides: 22% (4/18) vs. 0% (0/15); Patient decides, considering physician's opinion: 22% (4/18) vs. 53% (8/15); Both parties decide: 17% (3/18) vs. 7% (1/15); Physician decides, considering patient's opinion: 33% (6/18) vs. 40% (6/15); Physician decides: 6% (1/18) vs. 0% (0/15)	Time of year: November 2007-March 2008 Patterns of disease activity: NR Locally tailored: No (although intervention was iteratively refined during this pilot study) System-level characteristics: FMGs are organized through the Ministère de la Santé et des Services sociaux of Quebec and provide family medicine services to registered individuals	"Clinical practice guidelines (CPGs)" [Used for outcome of FPs' "Intention to comply with CPGs"; Not part of definition of antibiotic use or prescription outcomes]

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Légaré, 2010 Quebec, Canada Patient N = 459 (15 per clinician) Provider N = 33 Practice N = 4 (2 vs. 2)	Experimental group (EG) vs. Control group (CG) Patients who decided to use antibiotics immediately: Time T0: 56% vs. 54% Time T1: 33% vs. 49% Time T2: 35% vs. 46% Difference at T1; 95% CI: -16; 95% Cl, -31 to 1; p=0.08 Difference in Experimental group between T1 and T2 (indicating sustainability): 2 (-14 to 16) Difference between change in Experimental group (T0 to T2) and change in Control Group (T0 to T2): -13 (-39 to 6) Mean proportion of patients who filled prescription: Time T0: 79% vs. 70% Time T1: 45% vs. 51% Difference at T1; 95% CI: -6; 95% Cl, -17 to 6; p=0.35	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects	KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics
Légaré, 2010 Quebec, Canada Patient N = 459 (15 per clinician) Provider N = 33 Practice N = 4 (2 vs. 2)	NR	Experimental group vs. Control group Patients who felt they had stable, a little better or much better health at 2 weeks (vs. not much worse or much worse): Time T0: 87% vs. 91% Time T1: 94% vs. 85% Time T2: 94% vs. 91% Difference at T1; 95% CI: 9; 95% Cl, -2 to 18; p=0.08 Difference in Experimental group between T1 and T2 (indicating sustainability): 0 (-8 to 8) Difference between change in Experimental group (T0 to T2) and change in Control group (T0 to T2): 7 (-6 to 21)

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Légaré, 2010 Quebec, Canada Patient N = 459 (15 per clinician) Provider N = 33 Practice N = 4 (2 vs. 2)	Experimental group vs. Control group Correlation of FP's and patients' decisional conflict scale (DCS) scores (Pearson's *r*): Time T0: 0.14 vs. -0.05; Time T1: 0.24 vs. 0.02; Time T2: 0.17 vs. 0.18 Difference at T1; 95% CI: 0.26; 95% CI, -0.06 to 0.53; p=0.06 Difference in Experimental group between T1 and T2 (indicating sustainability): -0.1, -0.4 to 0.2 Difference between change Experimental group (T0 to T2) and change Control group (T0 to T2): -0.1 (CI not calculable) Quality of the decision (FPs), mean score (±SD): Time T0: 8.8 ± 1.1 vs. 8.3 ± 1.4; Time T1: 8.7 ± 1.2 vs. 8.5 ± 1.3; Time T2: 8.7 ± 1.1 vs. 8.5 ± 1.0 Difference at T1; 95% CI: 0.2; 95% CI, -0.34 to 0.89; p=0.29 Difference in Experimental group between T1 and T2 (indicating sustainability): 0, -0.4 to 0.2 Difference between change in Experimental group (T0 to T2) and change in Control group (T0 to T2): -0.3, -0.8 to 0.1 Quality of the decision (Patients), mean score (±SD): Time T0: 8.2 ± 2.1 vs. 8.4 ± 1.9; Time T1: 8.7 ± 1.9 vs. 8.6 ± 1.9; Time T2: 9.1 ± 2.1 vs. 8.1 ± 1.8 Difference at T1; 95% CI: 0.1; 95% CI, -0.88 to 0.94; p=0.57 Difference in Experimental group between T1 and T2 (indicating sustainability): 0.4, -0.2 to 1.1 Difference between change in Experimental group (T0 to T2) and change in Control group (T0 to T2): 1.2, 0.3 to 2.3 Patients with decisional regret: Time T0: 1% vs. 1%; Time T1: 7% vs. 9%; Time T2: 3% vs. 9% Difference at T1; 95% CI: -2; 95% CI, -12 to 5; p=0.91 Difference in Experimental group between T1 and T2 (indicating sustainability): -4, -22 to 7 Difference between change in Experimental group (T0 to T2) and change in Control group (T0 to T2): -6, -30 to 22	NR	

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Patient Population Criteria	Provider Population Criteria	Intervention Strategy Type: (1) Educational/Behavioral (2) Communication (3) Clinical (4) System-Level (5) Multifaceted Target of Intervention (patient, provider, etc.) Intervention Description
Légaré, 2010 Continued.			

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Comparator	Patient Characteristics: Type of RTI Types of Signs and Symptoms Duration of Signs and Symptoms When Counting Started for Duration	Patient Characteristics: Mean Age Percent Female Ethnicity Socioeconomic Status Educational level Frailty Comorbidities Prior RTIs Prior Use of Antibiotics
Légaré, 2010 Continued.			Educational level (college degree): 72% (57/81) vs.57% (39/70) Time T2 (n = 139, 72 vs. 67): Adults: 79% (57/72) vs.72% (48/67) Age, years (adults), mean ± SD: 40 ± 13 vs. 37 ± 11 Age, years (children), mean ± SD: 3 ± 3 vs. 5 ± 4 Female: 69% (50/72) vs.76% (51/67) SES (income ≥ Canadian $ 45,000/yr): 62% (41/72) vs.72% (44/67) SES (currently working): 70% (57/72) vs.87% (58/67) SES (with public drug insurance): 25% (18/72) vs.12% (8/67) Educational level (college degree): 61% (44/72) vs.63% (41/67) Ethnicity: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Provider Characteristics: Specialty Number of Years in Practice Type of Clinic Geographical Region Population Served	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness
Légaré, 2010 Continued.			

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Légaré, 2010 Continued.		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects	KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics
Légaré, 2010 Continued.		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Légaré, 2010 Continued.	Intention to engage in SDM (FPs), mean score (±SD): Time T0: 0.8 ± 0.8 vs. 0.3 ± 1.6; Time T1: 1.3 ± 1.2 vs. 0.8 ± 1.3; Time T2: 1.4 ± 0.7 vs. 0.7 ± 1.0 Difference at T1; 95% CI: 0.5; 95% Cl, -0.2 to 1.3; p=0.77 Difference in Experimental group between T1 and T2 (indicating sustainability): 0.1, -0.5 to 0.7 Difference between change in Experimental group (T0 to T2) and change in Control group (T0 to T2): 0.05, -0.9 to 1 Intention to engage in SDM (Patients), mean score (±SD): Time T0: 1.1 ± 1.4 vs. 0.8 ± 1.6; Time T1: 0.7 ± 1.2 vs. 0.8 ± 1.4; Time T2: 1.1 ± 1.5 vs. 0.7 ± 1.3 Difference at T1; 95% CI: -0.1; 95% Cl, -0.6 to 0.4; p=0.16 Difference in Experimental group between T1 and T2 (indicating sustainability): 0.4, -0.1 to 0.8 Difference between change in Experimental group (T0 to T2) and change in Control group (T0 to T2): 0.1, -0.5 to 0.7 Intention of FPs to comply with clinical practice guidelines, mean score (±SD): Time T0: 1.9 ± 0.8 vs. 1.8 ± 0.8; Time T1: 2.1 ± 0.9 vs. 2.2 ± 0.5; Time T2: 2.1 ± 0.7 vs. 2.0 ± 0.9 Difference at T1; 95% CI: -0.1; 95% Cl, -0.7 to 0.5; p=0.58 Difference in Experimental group between T1 and T2 (indicating sustainability): 0, -0.5 to 0.5 Difference between change in Experimental group (T0 to T2) and change in Control group (T0 to T2): 0, -0.6 to 0.7		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Légaré, 2012 Quebec, Canada Patient N = 359 (181 vs. 178) Provider N = 149 (77 vs. 72) Practice N = 9 (5 vs. 4) Légaré, 2013 Quebec, Canada Patient N = NR Provider N = 270 (250 completed entry questionnaire) Practice N = 12 (9 completed entry questionnaire)	Adult or child; Diagnosis of acute respiratory infection (e.g., bronchitis, OM, pharyngitis or rhinosinusitis) for which the use of antibiotics was subsequently considered either by patient or physician during the visit. Able to read, understand and write in French	Family practice teaching units (unit of randomization) affiliated with the Department of Family Medicine and Emergency Medicine at Université Laval in 6 regions of Quebec; Family physician (teacher or resident) and nurse practitioner; Providing care in department's walk-in clinics. Exclude: Participated in previous pilot trial of intervention; Not expecting to practice in teaching unit during the trial	Type: Communication Target: Providers Description: Two-hour on-line tutorial followed by a 2-hour on-site interactive workshop. On-line tutorial addressed key components of clinical decisionmaking process about antibiotic treatment for ARI in primary care. On-site workshop to help physicians review and integrate concepts from on-line training. Both tutorial and workshop included videos, exercises and decision aids to help physicians communicate to patients the probability of bacterial vs. viral URI and the benefits/harms associated with use of antibiotics.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Légaré, 2012 Quebec, Canada Patient N = 359 (181 vs. 178) Provider N = 149 (77 vs. 72) Practice N = 9 (5 vs. 4) Légaré, 2013 Quebec, Canada Patient N = NR Provider N = 270 (250 completed entry questionnaire) Practice N = 12 (9 completed entry questionnaire)	Randomized (at teaching unit level) control group physicians and patients seen by those physicians. Study was a parallel cluster RCT, in which the control group physicians were asked to provide usual care. Access to on-line tutorial denied to control group during trial	Intervention vs. Control Type of RTI: NR Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR Before Intervention: Preferred role in decisionmaking, % (n/N): Patient decides: 1.2% (2/171) vs. 5.4% (9/166); Patient decides, considering physician's opinion: 29.8% (51/171) vs. 22.9% (38/166); Both parties decide: 21.1% (36/171) vs. 29.5% (49/166); Physician decides, considering patient's opinion: 38.0% (65/171) vs. 36.1% (60/166); Physician decides: 9.9% (17/171) vs. 6.0% (10/166) After Intervention: Preferred role in decisionmaking, % (n/N): Patient decides: 3.7% (6/163) vs. 1.2% (2/165); Patient decides, considering physician's opinion: 28.2% (46/163) vs. 33.3% (55/165); Both parties decide: 32.5% (53/163) vs. 26.1% (43/165); Physician decides, considering patient's opinion: 30.1% (49/163) vs. 32.1% (53/165); Physician decides: 5.5% (9/163) vs. 7.3% (12/165)	Intervention vs. Control Before Intervention: Adults (≥ 18 y): 64.3% vs.77.8% Age, years (adults), mean ± SD: 39.3 ± 12.4 vs. 43.3 ± 16.2 Age, years (children), mean ± SD: 4.6 ± 3.8 vs. 5.0 ± 3.9 Female: 65.6% vs. 59.8% SES (with private drug insurance): 68.1% vs. 71.8% Educational level (college degree): 59.0% vs. 60.2% Comorbidities (≥ 1 chronic disease): 14.8% vs. 17.5% After Intervention: Adults (≥ 18 y): 60.9% vs.83.6% Age, years (adults), mean ± SD: 40.8 ± 15.1 vs. 43.3 ± 14.8 Age, years (children), mean ± SD: 4.9 ± 3.7 vs. 4.9 ± 4.1 Female: 64.6% vs.68.0% SES (with private drug insurance): 75.9% vs. 67.8% Educational level (college degree): 58.0% vs. 63.1% Comorbidities (≥ 1 chronic disease): 8.8% vs. 15.7% Ethnicity: NR Frailty: NR Prior RTIs: NR Prior use of antibiotics: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Légaré, 2012 Quebec, Canada Patient N = 359 (181 vs. 178) Provider N = 149 (77 vs. 72) Practice N = 9 (5 vs. 4) Légaré, 2013 Quebec, Canada Patient N = NR Provider N = 270 (250 completed entry questionnaire) Practice N = 12 (9 completed entry questionnaire)	Intervention vs. Control Specialty: Family Practice (both groups) Type of clinic: Academic Family Medicine (both groups) Geographical region: 6 regions of Quebec (both groups) Population served: General population (both groups) Before Intervention: Number of years in practice: Teachers (years) mean ± SD: 13.7 ± 10.1 vs. 15.6 ± 10.7 Resident year 1: 52.7% vs. 58.3% Resident year 2: 47.3% vs. 41.7% Preferred role in decisionmaking, % (n/N): Patient decides: 10.1% (15/149) vs. 8.1% (8/99); Patient decides, considering physician's opinion: 19.5% (29/149) vs. 14.1% (14/99); Both parties decide: 50.3% (75/149) vs. 47.5% (47/99); Physician decides, considering patient's opinion: 20.1% (30/149) vs. 30.3% (30/99); Physician decides: 0% (0/149) vs. 0% (0/99) After Intervention: Number of years in practice: Teachers (years) mean ± SD: 13.9 ± 10.3 vs. 15.2 ± 10.7 Resident year 1: 55.4% vs. 52.7% Resident year 2: 44.6% vs. 47.3% Preferred role in decisionmaking, % (n/N): Patient decides: 10.0% (16/160) vs. 8.3% (9/108); Patient decides, considering physician's opinion: 21.9% (35/160) vs. 14.8% (16/108); Both parties decide: 48.8% (78/160) vs. 46.3% (50/108); Physician decides, considering patient's opinion: 19.4% (31/160) vs. 30.6% (33/108); Physician decides: 0% (0/160) vs. 0% (0/108)	Time of year: July 2010 - April 2011; Intervention: November, 2010. Patterns of disease activity: NR Locally tailored: No	"Clinical practice guidelines (CPGs)" [Used for outcome of FPs' "Intention to comply with CPGs"; Not part of definition of antibiotic use or prescription outcomes]

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Légaré, 2012 Quebec, Canada Patient N = 359 (181 vs. 178) Provider N = 149 (77 vs. 72) Practice N = 9 (5 vs. 4) Légaré, 2013 Quebec, Canada Patient N = NR Provider N = 270 (250 completed entry questionnaire) Practice N = 12 (9 completed entry questionnaire)	Intervention vs. Control Proportion of patients who decided to use antibiotics immediately after consultation (All patients): Baseline: 41.2% vs. 39.2% After intervention: 27.2% vs. 52.2% Absolute difference: 25.0% Adjusted relative risk (adjusted for cluster design, baseline values, and patient age group): RR=0.5; 95% CI, 0.3 to 0.7 Proportion of patients who decided to use antibiotics immediately after consultation (Adults): Baseline: 41.9% vs. 39.8% After intervention: 26.6% vs. 50.7% Absolute difference: 24.1% Adjusted relative risk: RR=0.5; 95% CI, 0.4 to 0.8 Proportion of patients who decided to use antibiotics immediately after consultation (Children): Baseline: 40.0% vs. 36.8% After intervention: 27.1% vs. 65.5% Absolute difference: 38.4% Adjusted relative risk: RR=0.4; 95% CI, 0.3 to 0.7	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Légaré, 2012 Quebec, Canada Patient N = 359 (181 vs. 178) Provider N = 149 (77 vs. 72) Practice N = 9 (5 vs. 4) Légaré, 2013 Quebec, Canada Patient N = NR Provider N = 270 (250 completed entry questionnaire) Practice N = 12 (9 completed entry questionnaire)	NR	Intervention vs. Control Patient QOL (physical scale): Before intervention: 49.3 ± 8.8 vs. 47.7 ± 8.9 After intervention: 49.4 ± 7.5 vs. 48.2 ± 7.8 Mean difference: 0.4 (95% CI: -2.6 - 3.3) Patient QOL (mental scale): Before intervention: 51.2 ± 8.0 vs. 48.5 ± 11.0 After intervention: 50.8 ± 9.3 vs. 51.2 ± 8.4 Mean difference: -1.9 (95% CI: -4.9 - 1.1) Patient repeat consultation for same reason: Before intervention: 21.6% vs. 13.4% After intervention: 22.7% vs. 15.2% Adjusted RR (adjusted for cluster design and baseline values): RR=1.3; 95% CI, 0.7 to 2.3

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Légaré, 2012 Quebec, Canada Patient N = 359 (181 vs. 178) Provider N = 149 (77 vs. 72) Practice N = 9 (5 vs. 4) Légaré, 2013 Quebec, Canada Patient N = NR Provider N = 270 (250 completed entry questionnaire) Practice N = 12 (9 completed entry questionnaire)	Légaré, 2012: Intervention vs. Control Patient Decisional Conflict Scale (% with score ≥ 2.5): Before intervention: 5.1% vs. 4.2%; After intervention: 4.6% vs. 6.3%; Adjusted RR (adjusted for cluster design and baseline values): RR=0.8; 95% CI, 0.2 to 2.4 Patient quality of decision: Before intervention: 8.7 ± 1.5 vs. 8.7 ± 1.5; After intervention: 8.5 ± 1.6 vs. 8.5 ± 1.5; Mean difference: 0.0; 95% CI, -0.4 to 0.4 Patient intention to engage in SDM: Before intervention: 1.9 ± 1.2 vs. 2.0 ± 1.2; After intervention: 2.1 ± 1.1 vs. 1.9 ± 1.2; Mean difference: 0.2; 95% CI, -0.1 to 0.4 Patient adherence to decision: Before intervention: 91.6% vs. 88.4%; After intervention: 87.7% vs. 91.5%; Adjusted RR: RR=1.0; 95% CI, 0.9 to 1.0 Patient regret over decision: Before intervention: 10.5 ± 15.4 vs. 10.8 ± 20.8; After intervention: 12.4 ± 19.1 vs. 7.6 ± 13.7; Mean difference: 4.8; 95% CI, 0.9 to 8.7 Physician Decisional Conflict Scale (% with score ≥ 2.5): Before intervention: 4.5% vs. 3.0%; After intervention: 4.6% vs. 1.1%; Adjusted RR: RR=3.4; 95% CI, 0.3 to 38.0 Physician quality of decision: Before intervention: 8.2 ± 1.1 vs. 8.2 ± 1.4; After intervention: 8.2 ± 1.3 vs. 8.4 ± 1.0; Mean difference: -0.2; 95% CI, -0.6 to 0.2 Physician intention to engage in SDM: Before intervention: 1.6 ± 0.8 vs. 1.6 ± 0.9; After intervention: 1.7 ± 0.9 vs. 1.8 ± 0.7; Mean difference: 0.0; 95% CI; -0.3 to 0.2 Physician intention to follow clinical practice guidelines: Before intervention: 2.2 ± 0.6 vs. 2.2 ± 0.7; After intervention: 2.0 ± 0.7 vs. 2.2 ± 0.7; Mean difference: -0.2; 95% CI, -0.5 to 0.1	NR	

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Patient Population Criteria	Provider Population Criteria	Intervention Strategy Type: (1) Educational/Behavioral (2) Communication (3) Clinical (4) System-Level (5) Multifaceted Target of Intervention (patient, provider, etc.) Intervention Description
Légaré, 2012 Légaré, 2013 Quebec, Canada Continued			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Légaré, 2012 Légaré, 2013 Quebec, Canada Continued			

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Provider Characteristics: Specialty Number of Years in Practice Type of Clinic Geographical Region Population Served	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness
Légaré, 2012 Légaré, 2013 Quebec, Canada Continued	Preferred role in decisionmaking, % (n/N): Patient decides: 4% (4/92) vs. 4% (3/73); Patient decides, considering physician's opinion: 32% (29/92) vs. 33% (24/73); Both parties decide: 34% (31/92) vs. 19% (14/73); Physician decides, considering patient's opinion: 17% (16/92) vs. 33% (24/73); Physician decides: 13% (12/92) vs. 11% (8/73) Legare, 2013: Teachers (years) mean ± SD: 13.9 ± 10.3 vs. 15.2 ± 10.7		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ1 outcomes: Appropriate prescription and use of antibiotics	KQ2 outcomes: Antibiotic resistance
Légaré, 2012 Légaré, 2013 Quebec, Canada Continued		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects	KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics
Légaré, 2012 Légaré, 2013 Quebec, Canada Continued		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Légaré, 2012 Légaré, 2013 Quebec, Canada Continued	Legare, 2013: Shared decision making behaviors Entry vs. Exit: mean ± SD D-Option (patient) Intervention vs. Control: 79.3 ± 1.4 vs. 80.0 ± 1.5; 80.1 ± 1.1 vs. 74.9 ± 1.1, p-value = 0.001 D-Option (physician) Intervention vs. Control: 74.4 ± 2.1 vs. 75.5 ± 1.7; 79.7 ± 1.8 vs. 76.3 ± 1.9, p-value = 0.20 Assumed role (patient): p-value = 0.04 Active/collaborative role n (%): 101 (55.5) vs. 99 (57.9); 118 (67.1) vs. 87 (49.2) Passive role n (%): 81 (44.5) vs. 72 (42.1); 58 (32.9) vs. 90 (50.8) Intention to engage in shared decision making and its related determinants at study entry and exit: Theory of Planned Behavior (TPB) constructs Entry vs. Exit: Intention Intervention vs. control mean ± SD: 1.6 ± 0.1 vs. 1.5 ± 0.1; 1.7 ± 0.1 vs. 1.8 ± 0.1, Mean Difference = 0.1, p-value = 0.74 Instrumental attitude Intervention vs. control: 1.9 ± 0.1 vs. 1.9 ± 0.1; 2.2 ± 0.1 vs. 2.2 ± 0.1, Mean Difference = 0, p-value = 0.97 Affective attitude Intervention vs. control: 1.3 ± 0.1 vs. 1.1 ± 0.2; 1.6 ± 0.1 vs. 1.4 ± 0.1, Mean Difference = 0.2, p-value = 0.19 Subjective norm Intervention vs. control: 1.5 ± 0.1 vs. 1.4 ± 0.1; 1.6 ± 0.1 vs. 1.7 ± 0.1, Mean Difference = 0.1, p-value = 0.55 Perceived behavioral control Intervention vs. control: 1.2 ± 0.1 vs. 1.1 ± 0.1; 1.3 ± 0.1 vs. 1.3 ± 0.1, Mean Difference = 0, p-value = 0.99		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Linder, 2009 United States Patient N = 111,820 Provider N = 443 Practice N = NR	Acute respiratory infections	Randomly assigned 27 PCP clinics that use their EHR, matched for size, to intervention (ARI smart form) vs. control	Type: System-level Target: Providers Description: 27 primary care clinics were randomized to receive an EHR-integrated, documentation-based clinical decision support system for the care of patients with ARIs ("ARI Smart Form") or to offer usual care.
Linder, 2010 United States Patient N = 136,633 Provider N = 573 Practice N = NR	Acute respiratory infections	Randomly assigned 27 PCP clinics that use their EHR, matched for size, to intervention (ARI quality dashboard) vs. control	Type: System-level Target: Providers Description: 27 primary care clinics were randomized to receive an EHR-based feedback system ("ARI Quality Dashboard") or usual care.
Little, 1997 (Please refer to Spurling, 2013 systematic review)			
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Linder, 2009 United States Patient N = 111,820 Provider N = 443 Practice N = NR	No decision tool	Type of RTI: any URI (called ARI---acute) Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Control vs. Intervention Mean Age: 48 years vs. 49 years % female 69% vs. 61% Ethnicity: 59% white vs. 48% All other characteristics: NR
Linder, 2010 United States Patient N = 136,633 Provider N = 573 Practice N = NR	No decision tool	Types of RTI: pneumonia, strep pharyngitis, sinusitis, OM, nonstrep pharyngitis, influenza, acute bronchitis, and nonspecific URI All other characteristics: NR	NR
Little, 1997 (Please refer to Spurling, 2013 systematic review)			
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Linder, 2009 United States Patient N = 111,820 Provider N = 443 Practice N = NR	Control vs. Intervention Physicians Specialty: 54% vs. 44% staff physicians All other characteristics: NR	Time of year: November 2005- May 2006 Patterns of disease activity: NR Locally tailored: Tailored to electronic health record users System-level characteristics: NR	Used appropriateness in secondary outcome measures---appropriate conditions for antibiotics use included strep pharyngitis, pneumonia, sinusitis, and otitis media. Others were not appropriate
Linder, 2010 United States Patient N = 136,633 Provider N = 573 Practice N = NR	Specialty: 60% staff physicians All other characteristics: NR	Time of year: November 2006-August 2007 Patterns of disease activity: NR Locally tailored: Tailored to electronic health record users System-level characteristics: NR	Used appropriateness in secondary outcome measures---appropriate conditions (based on ICD-9 code) for antibiotic use included strep pharyngitis, pneumonia, sinusitis, and otitis media. Others were not appropriate
Little, 1997 (Please refer to Spurling, 2013 systematic review)			
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Linder, 2009 United States Patient N = 111,820 Provider N = 443 Practice N = NR	Primary outcome measure was antibiotic prescription for ARIs Control vs intervention: 43% vs 39%, OR=0.8; 0.6 to 1.2; p=0.30 in per-protocol analysis (as used) 59% versus 88% [OR calculated the other direction 5.0 and statistically significant] overall antibiotic use for acute bronchitis (no designation of appropriateness) was 61% versus 45% [OR calculated the other direction 0.5; 0.3 to 0.9. Only in 6% of ARI visits was the intervention tool "ARI smart form" used within the intervention clinics.	NR
Linder, 2010 United States Patient N = 136,633 Provider N = 573 Practice N = NR	Primary outcome measure was antibiotic prescription for ARIs Control vs intervention: 47% versus 47%, and for antibiotic appropriate conditions 64% versus 65%. In per protocol analysis (among users of the ARI tool) this was 42% overall and 63% for antibiotic appropriate conditions. When limiting analysis to intervention practices in comparing users and non-users of the tool, there was slight decrease in antibiotic use overall 42% versus 50%, p=0.02, but no difference in antibiotic use in antibiotic appropriate conditions (so this small difference was driven by decrease in inappropriate antibiotic use)	NR
Little, 1997 (Please refer to Spurling, 2013 systematic review)		
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Linder, 2009 United States Patient N = 111,820 Provider N = 443 Practice N = NR	NR	30 day revisit rate control 26% vs. intervention 23% 30 day revisit rate attributable to ARI control 9% vs. intervention 8%
Linder, 2010 United States Patient N = 136,633 Provider N = 573 Practice N = NR	NR	NR
Little, 1997 (Please refer to Spurling, 2013 systematic review)		
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Linder, 2009 United States Patient N = 111,820 Provider N = 443 Practice N = NR	NR	NR	
Linder, 2010 United States Patient N = 136,633 Provider N = 573 Practice N = NR	NR	NR	
Little, 1997 (Please refer to Spurling, 2013 systematic review)			
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Little, 2013 United Kingdom Patient N = 1,129 (Score 1), 631 (FeverPAIN, Score 2) Provider N = NR Practice N = 48	Patients were people aged ≥ 3 presenting with acute sore throat (two weeks or less of sore throat) and an abnormal looking throat (e.g. erythema and/or pus)	General practitioners and triage practice nurses in general practices in south and central England	Type: Clinical - POC: Rapid Strep Target: Provider Description: Intervention groups included (1) Clinical score and (2) Rapid antigen detection testing. FeverPAIN score was applied to clinical score group and antibiotics were not offered to those with low scores (0/1). Immediate antibiotics offered for those with high scores (≥ 4, an estimated 63% streptococci based on diagnostic studies). Delayed antibiotics were given to those with intermediate scores (2 or 3, 39% streptococci). The clinical score was used in all patients in the rapid antigen test group. Those with low clinical scores (0/1) were not offered antibiotics or a rapid antigen test (< 20% streptococci). Those with a score of 2 (33% streptococci) were offered a delayed prescription. Those with higher scores (≥ , 55% streptococci) underwent rapid antigen test in clinic. Patients with negative results were not offered antibiotics. IMI test pack RADT was used based on in vitro performance and ease of use

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Little, 2013 United Kingdom Patient N = 1,129 (Score 1), 631 (FeverPAIN, Score 2) Provider N = NR Practice N = 48	Delayed antibiotics (control). Patient was advised to collect prescription after 3 to 5 days if symptoms did not improve or became considerably worse	Type of RTI: Streptococcal sore throat Types of Signs and Symptoms: fever in the past 24 hours (56.7%), pus on tonsils (25.8%) Duration of Signs and Symptoms: 4.8 days When counting started for duration: NR	Mean Age: 29.7 years % female: 64.2% Ethnicity: NR SES: NR Educational: NR Frailty: NR Comorbidities: NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Provider Characteristics: Specialty Number of Years in Practice Type of Clinic Geographical Region Population Served	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness
Little, 2013 United Kingdom Patient N = 1,129 (Score 1), 631 (FeverPAIN, Score 2) Provider N = NR Practice N = 48	Specialty: General practice Numbers of years in practice: NR Type of clinic: General practice Geographical area: South and central England	Time of year: October 2008 to April 2011 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Little, 2013 United Kingdom Patient N = 1,129 (Score 1), 631 (FeverPAIN, Score 2) Provider N = NR Practice N = 48	Delayed prescribing (control) vs. Clinical score (FeverPAIN) only vs. Clinical score (FeverPAIN) + rapid antigen test Antibiotic Use, crude %, risk ratio; 95% CI; p: 46%; RR=1.00 vs. 37%; RR=0.71; 95% CI, 0.50 to 0.95; p=0.02 vs. 35%; RR=0.73; 95% CI, 0.52 to 0.98; p=0.03 Delayed prescribing (control) vs. Clinical score (Score 1) only vs. Clinical score (Score 1) + rapid antigen test Antibiotic Use, crude %, risk ratio (95% CI), P: 39%; RR=1.00 vs. 47 %; RR=1.20; 95% CI, 0.99 to 1.42; p=0.059 vs. 35%; RR=0.88; 95% CI, 0.69 to 1.09; p=0.265	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects	KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics
Little, 2013 United Kingdom Patient N = 1,129 (Score 1), 631 (FeverPAIN, Score 2) Provider N = NR Practice N = 48	NR	Delayed prescribing (control) vs. Clinical score (FeverPAIN) only vs. Clinical score (FeverPAIN) + rapid antigen test Return visits within 1 month with sore throat: 8%; RR=1.00 vs. 8%; RR=0.91; 95% CI, 0.47 to 1.72; p=0.78 vs. 6%; RR=0.74; 95% CI, 0.36 to 1.47; p=0.40 Return visits after 1 month with sore throat (mean followup 0.73 years): 15%, RR=1.00 vs. 12%; RR=0.79; 95% CI, 0.47 to 1.29; p=0.35 vs. 16%; RR=1.06; 95% CI ,0.66 to 1.63; p=0.81 Mean severity of sore throat and difficulty swallowing days on days 2-4*, crude mean (SD), adjusted mean difference: 3.11 (1.49) vs. 2.88 (1.52), -0.33, -0.64 to -0.02; p=0.04 vs. 2.83 (1.62), -0.30, -0.61 to 0.004; p=0.05 Duration of symptoms rated moderately bad or worse (days), mean duration (IQR), HR; 95% CI: 5 (3-7), HR=1.00 vs. 4 (2-6), HR=1.30; 95% CI,1.03 to 1.63; p=0.03) vs. 4 (2-7), HR=1.11; 95% CI, 0.88 to 1.40; p=0.37 Delayed prescribing (control) vs. Clinical score (Score 1) only vs. Clinical score (Score 1) + rapid antigen test Return visits within 1 month with sore throat: 11%, RR=1.00 vs. 9%, RR=0.76; 95% CI, 0.49 to 1.16, p=0.205 vs. 13%, RR=1.11; 95% CI, 0.74 to 1.62, p=0.618 Return visits after 1 month with sore throat (mean followup 0.73 years): 20%, RR=1.00 vs. 22%, RR=1.10; 95% CI, 0.83 to 1.44; p=0.488 vs. 19%, RR=0.95; 95% CI, 0.70 to 1.27; p=0.728 Mean severity of sore throat and difficulty swallowing days on days 2-4*, crude mean (SD), adjusted mean difference: 2.95 (1.44) vs. 3.05 (1.49), 0.06, -0.15 to 0.28; p=0.560 vs. 2.83 (1.50), -0.12, -0.34 to 0.10; p=0.270 Duration of symptoms rated moderately bad or worse, HR; 95% CI: HR=1.00 vs. HR=0.95; 95% CI, 0.80 to 1.13; p=0.543 vs. HR=1.10; 95% CI, 0.92 to 1.31; p=0.282

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Little, 2013 United Kingdom Patient N = 1,129 (Score 1), 631 (FeverPAIN, Score 2) Provider N = NR Practice N = 48	NR	NR	*7 point scale: 0 = no problem, 6 = as bad as it could be

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Little, 2013 Multinational Patient N = 6771 (baseline), 4264 (followup period) Provider N = 372; Practice N= 246 randomized; 228 contributing data (during followup period) Yardley, 2013 Patient N = 4,264 recruited; 2,886 completed the self-report measures Provider N = 424; 346 completed the self-report measures at baseline, followup, or both time points Practice N = 229	Age older than 18 years; first consultation for acute cough of up to 28 days' duration or what the clinician believed to be an acute LRTI as the main diagnosis, despite cough not being the most prominent symptom; and diagnosis judged by physician to be an acute URTI (e.g. sore throat, otitis media, sinusitis, influenza, and coryzal illness). Up to first 30 LRTI and up to first five URTI to present at each practice were recruited	Providers in eligible practices that had not previously used any interventions to reduce antibiotic prescribing rates and could include more than ten patients in baseline audit	Type: Multifaceted - POC: CRP and Enhanced Communication Skills Training Target: Providers Description: Three intervention groups: (1) CRP group, (2) communication training, and (3) CRP + communication training. CRP group received internet training on how to target testing and how to negotiate with patient about management decisions. CRP tests done with QuikRead CRP kits after on-site training by manufacturer. Training in enhanced communication skills focused on gathering information on patients' concerns and expectations, exchange of information on symptoms, natural disease course, and treatments, agreement of a management plan, summing up and providing guidance about when to reconsult. Physicians also provided with interactive booklet to use during consultations

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Little, 2013 Multinational Patient N = 6771 (baseline), 4264 (followup period) Provider N = 372; Practice N= 246 randomized; 228 contributing data (during followup period) Yardley, 2013 Patient N = 4,264 recruited; 2,886 completed the self-report measures Provider N = 424; 346 completed the self-report measures at baseline, followup, or both time points Practice N = 229	Usual care (control)	Type of RTI: LRTI (79.7%), other RTI (20.3%) Types of Symptoms: Sputum production (81.2%) Duration of Signs and Symptoms: 7.73 days (mean duration of illness before index consultation) When counting started for duration: NR	Mean Age: 51 years % Female: 64.1% Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: Lung disease including COPD or asthma (18.2%) Prior RTIs: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Little, 2013 Multinational Patient N = 6771 (baseline), 4264 (followup period) Provider N = 372; Practice N= 246 randomized; 228 contributing data (during followup period) Yardley, 2013 Patient N = 4,264 recruited; 2,886 completed the self-report measures Provider N = 424; 346 completed the self-report measures at baseline, followup, or both time points Practice N = 229	Specialty: Primary care Type of clinic: Primary care practices Geographical region: Multinational (Europe) Population served: NR Yardley, 2013: Number of years in practice: 19.22 y (± 9.63)	Time of year: October to December 2010 (baseline audit); internet training intervention followed by repeat audit (February to May 2011) Patterns of disease activity: Randomization, internet training, and repeat audit of antibiotic prescribing occurred at the end of the season for RTIs Locally tailored: NR System level characteristics: NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Little, 2013 Multinational Patient N = 6771 (baseline), 4264 (followup period) Provider N = 372; Practice N= 246 randomized; 228 contributing data (during followup period) Yardley, 2013 Patient N = 4,264 recruited; 2,886 completed the self-report measures Provider N = 424; 346 completed the self-report measures at baseline, followup, or both time points Practice N = 229	Little, 2013: Antibiotic Prescribing Rate, RR; 95% CI; p: No CRP training vs. CRP training Crude %: 48 vs. 33 Adjusted risk ratio: RR=1.00 vs. RR=0.54; 95% CI, 0.42 to 0.69); p<0.0001 Antibiotic Prescribing Rate, RR; 95% CI; p: No communication training vs. Communication training Crude %: 45 vs. 36 Adjusted* risk ratio: RR=1.00 vs. R=0.69; 95% CI, 0.54 to 0.87; p<0.0001 Antibiotic Prescribing, RR; 95% CI; p: CRP Group vs. Usual Care: RR=0.53; 95% CI, 0.36 to 0.74; p<0.0001 Communication Group vs. Usual Care: RR=0.68; 95% CI, 0.50 to 0.89; p=0.003 CRP + Communication Group vs. Usual Care: RR=0.38; 95% CI, 0.25 to 0.55; p<0.0001	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Little, 2013 Multinational Patient N = 6771 (baseline), 4264 (followup period) Provider N = 372; Practice N= 246 randomized; 228 contributing data (during followup period) Yardley, 2013 Patient N = 4,264 recruited; 2,886 completed the self-report measures Provider N = 424; 346 completed the self-report measures at baseline, followup, or both time points Practice N = 229	Little, 2013: Usual Care vs. CRP Group vs. Communication Group vs. CRP + Communication Group Hospital admissions (total n=30): 2 vs. 10 vs. 6 vs. 12 CRP Group vs. Non-CRP Group, OR; 95% CI; p: Controlling for clustering: OR=2.61; 95% CI, 1.07 to 6.35; p=0.034 Controlling for all potential confounders: OR=2.91; 95% CI, 0.96 to 8.85; p=0.060	Little, 2013: No CRP Training vs. CRP Training New or worse symptoms: Crude %: 18 vs. 19 Adjusted RR; 95% CI; p: RR=1.00 vs. RR=1.05; 95% CI, 0.78 to 1.39; p=0.76 Symptom severity score days 2-4 after index consultation: Crude mean (SD): 1.79 (0.99) vs. 1.79 (1.01) Adjusted mean difference, 95% CI; p: 0; 95% CI, -0.09 to 0.09; p=0.99 Resolution of symptoms rated moderately bad or worse: Crude median (IQR) time (days): 5 (3 to 9) vs. 5 (3 to 9) Adjusted hazard ratio; 95% CI; p: HR=1.00 vs. HR=0.93; 95% CI, 0.83 to 1.04, p=0.21 No Communication Training vs. Communication Training New or worse symptoms: Crude %: 16 vs. 20 Adjusted RR; 95% CI; p: RR=1.00 vs. RR=1.33; 95% CI, 0.99 to 1.74; p=0.055 Symptom severity score days 2-4 after index consultation: Crude mean (SD): 1.73 (0.98) vs. 1.84 (1.02) Adjusted mean difference; 95% CI; p: 0.07; 95% CI, -0.03 to 0.16; p=0.16 Resolution of symptoms rated moderately bad or worse: Crude median (IQR) time (days): 5 (3 to 7) vs. 6 (3 to 10) Adjusted hazard ratio; 95% CI; p: HR=1.00 vs. HR=0.83; 95% CI, 0.74 to 0.93; p=0.002

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Little, 2013 Multinational Patient N = 6771 (baseline), 4264 (followup period) Provider N = 372; Practice N= 246 randomized; 228 contributing data (during followup period) Yardley, 2013 Patient N = 4,264 recruited; 2,886 completed the self-report measures Provider N = 424; 346 completed the self-report measures at baseline, followup, or both time points Practice N = 229	Yardley, 2013: CRP group (baseline vs. followup) vs. Communication group (baseline vs. followup) vs. Combined group (baseline vs. followup) Importance of reducing prescribing: 6.03 vs. 6.22, 5.85 vs. 6.34, 5.90 vs. 6.25 Risks of reducing prescribing: 4.37 vs. 4.88, 4.81 vs. 5.16, 4.33 vs. 4.76 Risk to relationship with patients: 4.49 vs. 4.63, 4.74 vs. 4.89, 4.76 vs. 5.12 Confidence to reduce prescribing: 4.89 vs. 4.64, 4.71 vs. 5.12, 4.86 vs. 5.28 Usual care vs. CRP group vs. Communication group vs. Combined group Taking antibiotics is usually necessary: 4.13 vs. 3.75 vs. 4.02 vs. 3.83 Taking antibiotics can do more harm than good: 3.93 vs. 4.12 vs. 4.10 vs. 4.13 Patient enablement instrument: 5.12 vs. 5.00 vs. 5.19 vs. 5.11 Satisfaction with consultation: 5.85 vs. 5.76 vs. 5.95 vs. 5.89 *Scores are on a scale from 1 (disagree strongly) to 7 (agree strongly)	NR	*Adjusted risk ratio controlled for age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, crepitation, wheeze, pulse higher than 100 beats per minute, temperature higher than 37.8° C, respiratory rate, blood pressure, physician's rating of severity, and duration of cough

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Little, 2014 United Kingdom Patient N = 889 (556 in randomized trial) Provider N = 53 Practice N = 25	Aged 3 years and over with acute respiratory tract infection in a general practice setting.	Doctors and practice nurses	Type: Clinical Target: Providers Description: Nonrandomized group received immediate antibiotics. If antibiotics were not needed, patients were randomized to one of four delayed prescribing groups (recontact for a prescription, post-dated prescription, collection of the prescription, or patient led). Each group was randomized further into 12 subgroups according to three factors (antipyretic regimens (ibuprofen, paracetamol, or both combined), regular antipyretic versus "as required" dosing, and steam inhalation advice versus no advice to inhale with steam.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Little, 2014 United Kingdom Patient N = 889 (556 in randomized trial) Provider N = 53 Practice N = 25	No antibiotic prescription (randomized comparison)	Type of RTI: Lower respiratory infection (15.4%), pharyngitis or sore throat (26.3%), upper respiratory infection (37.0%) Types of signs and symptoms: acute cold, influenza, sore throat, otitis media, sinusitis, croup, or LRTI Duration of signs and symptoms: 7.2 days (previous duration) When counting started for duration: NR	Mean age: 32.2 % female: 61.4% Ethnicity: NR SES: NR Educational status: NR Frailty: NR Comorbidities: NR Prior RTIs: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Little, 2014 United Kingdom Patient N = 889 (556 in randomized trial) Provider N = 53 Practice N = 25	Specialty: General practice Number of years in practice: NR Type of clinic: Primary care Population served: NR	Time of year: March 3, 2010 to March 28, 2012 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Little, 2014 United Kingdom Patient N = 889 (556 in randomized trial) Provider N = 53 Practice N = 25	No Antibiotics vs. Recontact vs. Post-date vs. Collection vs. Patient led Antibiotic use, % of patients, adjusted* RR; 95% CI; p: 26 vs. 37, RR=1.45; 95% CI, 0.95 to 2.03; p=0.083 vs. 37, RR=1.41; 95% CI, 0.92 to 1.98; p=0.108 vs. 33, RR=1.28; 95% CI, 0.80 to 1.87; p=0.275 vs. 39, RR=1.52; 95% CI, 1.00 to 2.10; p=0.050 Likelihood ratio test $\chi 2$: 4.96, p=0.292	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Little, 2014 United Kingdom Patient N = 889 (556 in randomized trial) Provider N = 53 Practice N = 25	No Antibiotics vs. Recontact vs. Post-date vs. Collection vs. Patient led Side effects and complications (%) Diarrhea: 13 vs. 7 vs. 15 vs. 16 vs. 21 Rash: 8 vs. 5 vs. 8 vs. 2 vs. 9 Vomiting: 15 vs. 9 vs. 13 vs.. 4 vs.. 18 Abdominal pain: 25 vs. 10 vs. 18 vs. 29 vs. 31 Complications: 2.5 vs. 3.7 vs. 0.9 vs. 1 vs. 0	No Antibiotics vs. Recontact vs. Post-date vs. Collection vs. Patient led Reconsultation within 1 month, % of patients, adjusted* RR; 95% CI; : 16 vs. 18, RR=1.06; 95% CI, 0.56 to 1.84; p=0.853 vs. 10, RR=0.59; 95% CI, 0.27 to 1.21, p=0.159 vs. 14, RR=0.84; 95% CI, 0.43 to 1.57; p=0.618 vs. 14, RR=0.91; 95% CI, 0.47 to 1.65; p=0.772 Likelihood ratio test χ2: 2.97, p=0.563 Reconsultation after 1 month, % of patients, adjusted* RR; 95% CI; p: 32 vs. 39, RR=1.20; 95% CI, 0.80 to 1.66; p=0.354 vs. 39, RR=1.28; 95% CI, 0.87 to 1.74); p=0.189 vs. 32, RR=0.91; 95% CI, 0.55 to 1.35; p=0.652 vs. 37, RR=1.20; 95% CI, 0.80 to 1.65; p=0.358 Likelihood ratio test χ2: 4.11, p=0.391 Patient very satisfied with consultation, % of patients, adjusted* RR; 95% CI; p: 79 vs. 74, RR=0.93; 95% CI, 0.59 to 1.14; p=0.615 vs. 80, RR=0.99; 95% CI, 0.68 to 1.16; p=0.930 vs. 88, RR=1.09; 95% CI, 0.77 to 1.22; p=0.476 vs. 89, RR=1.12; 95% CI, 0.83 to 1.22; p=0.319 Likelihood ratio test χ2: 2.38; p=0.667 Symptom Improvement: Mean symptom severity, days 2-4, crude mean, adjusted* mean difference; 95% CI: 1.62 (0.88) vs. 1.60 (0.91), -0.01; -0.24 to 0.23; p=0.964 vs. 1.82 (0.94), 0.14; -0.10 to 0.37; p=0.249 vs. 1.68 (0.88), -0.02, -0.27 to 0.22; p=0.850 vs. 1.75 (0.88), 0.08; -0.16 to 0.33; p=0.499 Likelihood ratio test χ2: 2.61, p=0.625 Symptoms rated as moderately bad, mean duration (IQR), adjusted* hazard ratio, 95% CI: 3 (2-6.5) vs. 4 (3-7), 0.91; 0.66 to 1.25; p=0.561 vs. 4 (3-7), 0.86; 0.63 to 1.17; p=0.338 vs. 4 (3-7), 0.86; 0.62 to 1.20; p=0.380 vs. 4 (3-7), 0.71; 0.50 to 0.99; p=0.045 Likelihood ratio test χ2: 4.29, p=0.368

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Little, 2014 United Kingdom Patient N = 889 (556 in randomized trial) Provider N = 53 Practice N = 25	NR	NR	* all models controlled for baseline symptom severity, dosing, steam, and smoking.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Llor, 2011 Spain Patient N= 543 Provider N= 61 Practice N= 20	Patients with acute pharyngitis aged 14-60 years with at least 1 Centor criterion (fever, tonsillar exudate, tender enlarged anterior cervical lymph nodes, or absence of cough)	Primary care physicians	Type: Clinical - POC: Rapid Strep Target: Providers Description: Physicians allocated to intervention group were provided with RADT. RADTs were undertaken with the OSOM(R) Strep A test (Genzyme). All study physicians sent a pharyngeal swab for culture. A culture was considered positive for GABHS with a growth of any number of beta-hemolytic colonies, Gram staining with streptococcal morphology, and a catalase-negative test with posterior identification with an automated panel for WIDER Gram-positive cocci. Validity of rapid antigen test depending on Centor criteria (total, n=276): % group A beta-hemolytic streptococcus: 17.8; sensitivity 89.8%; specificity 93.8%; positive predicative value 75.9%; negative predictive value 97.7%.
MacFarlane, 2002 United Kingdom Patient N = 259 Provider N = NR Practice N = 3	Previously well adults (aged ≥ 16 years) not under supervision or management for an underlying disease, presenting with acute bronchitis, defined as a new acute lower respiratory tract illness in a previously well adult using the following previously reported definitions: lower respiratory tract illness required all of (1) acute illness present for 21 days or less, (2) cough as the main symptom, (3) at least one other lower respiratory tract symptom (sputum production, dyspnea, wheeze, chest discomfort or pain), (4) no alternative explanation	General practitioners working in three suburban general practices in Nottingham	Type: Multifaceted Target: Patients Description: General practitioners managed patients according to their usual clinical practice and judgment and divided patients into the following two groups: (1) Group A, in which antibiotics were not definitely indicated that day, and (2) Group B, in which antibiotics were definitely indicated that day. All patients were given a prescription for an antibiotic of the general practitioner's choice. Patients in Group B were advised to take the antibiotics. Patients in Group A received verbal information based on prompt card, then randomized using permuted blocks of four to receive or not receive patient information leaflet about natural course of lower respiratory tract symptoms and advantages/disadvantages of antibiotic use

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Llor, 2011 Spain Patient N= 543 Provider N= 61 Practice N= 20	Control (managed streptococcal pharyngitis with only clinical criteria)	Type of RTI: Acute pharyngitis Types of Signs and Symptoms: Fever (71.6%), tonsillar exudate (51.7%), tender cervical lymph nodes (40.5%), absence of cough (74.8%) Duration of Signs and Symptoms: NR When counting starting duration: NR	Mean Age: 31.7 years % female: 62.8 Ethnicity: NR SES: NR Educational level: NR Frailty: NR
MacFarlane, 2002 United Kingdom Patient N = 259 Provider N = NR Practice N = 3	No information leaflet (control)	Type of RTI: Acute bronchitis Types of Signs and Symptoms: Sputum (23.6% clear, 61.3 colored), findings of chest examination (17.5% general signs, 2.8% focal signs) Duration of Signs and Symptoms: 7 days (mean duration of cough) When counting started for duration: NR	Mean Age: 44.5 years % female: 62 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Llor, 2011 Spain Patient N= 543 Provider N= 61 Practice N= 20	Specialty: Primary care Number of years in practice: NR Type of clinic: Primary care centers Geographical region: Catalonia, Spain Population served: NR	Time of Year: January to May 2008 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	Inappropriateness based on Centor score (1-4)
MacFarlane, 2002 United Kingdom Patient N = 259 Provider N = NR Practice N = 3	Specialty: General practice Number of years in practice: NR Type of clinic: General practice Geographical region: Nottingham, UK Population served: NR	Time of year: September 1999 to August 2000 Patterns of disease activity: NR Locally tailored: Yes System level characteristics: NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Llor, 2011 Spain Patient N= 543 Provider N= 61 Practice N= 20	Intervention group (RADT) vs. Control Prescription of antibiotics according to Centor criteria (total): 43.8 % vs. 64.1%; p<0.001 Inappropriateness of antibiotic prescription according to Centor criteria (total): 26.9% vs. 60.0%; p<0.001	NR
MacFarlane, 2002 United Kingdom Patient N = 259 Provider N = NR Practice N = 3	Intervention (Leaflet) vs. Control (No Leaflet) % of patients taking antibiotics one or two weeks after consultation: 47.1 vs. 62.4	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Llor, 2011 Spain Patient N= 543 Provider N= 61 Practice N= 20	NR	NR
MacFarlane, 2002 United Kingdom Patient N = 259 Provider N = NR Practice N = 3	NR	Intervention (Leaflet) vs. Control (No Leaflet) % of patients reconsulted within four weeks of initial consultation: 10.6 vs. 13.3

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Llor, 2011 Spain Patient N= 543 Provider N= 61 Practice N= 20	NR	NR	
MacFarlane, 2002 United Kingdom Patient N = 259 Provider N = NR Practice N = 3	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)			
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)			
Maltezou, 2008 Greece Patient N = 820 Provider N = 24 Practice N = NR	Children aged 2-14 with clinical evidence of pharyngitis including one of the following four criteria: fever (>38.0 C), tonsillar exudate, tender enlarged cervical lymph nodes, and absence of cough	Pediatricians	Type: Clinical - POC: Rapid Strep Target: Providers Description: Two intervention groups: (1) Group B, includes diagnosis by RADT + culture, conducted by private practice pediatricians, and (A) Group C, includes diagnosis by RADT + culture, conducted by hospital affiliated pediatricians. Two throat swabs were taken; 1 swab tested by RADT by pediatrician at office or outpatient clinic, 1 swab sent to Infectious Disease Research Laboratory of the 4th Department of Internal Medicine (University General Hospital ATTIKON). Pediatricians informed patients of culture results and gave instructions regarding antibiotic, if required. Becton-Dickinson Link 2 Strep A Rapid test for streptococcal pharyngitis with culture was used. Sensitivity, specificity, and positive and negative predictive values of the rapid antigen detection test were 83.1%, 93.3%, 82.4%, and 93.6%, respectively
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)			
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)			
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)			
Maltezou, 2008 Greece Patient N = 820 Provider N = 24 Practice N = NR	Group A (clinical diagnosis ± empirical antibiotics, conducted by private practice pediatricians)	Type of RTI: streptococcal acute pharyngitis Types of symptoms: Fever (89.0%), tonsillar exudate (37.7%), tender cervical lymph nodes (41.8%), absence of cough (65.9%), conjunctivitis (4.5%), rash (5.1%), enanthema (39.5%), pharyngeal pain (86.7%), rhinorrhea (26.7%) Duration of Signs and symptoms: NR When counting started for duration: NR	Mean Age: 7.2 % Female: 52.1 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)			
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)			
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)			
Maltezou, 2008 Greece Patient N = 820 Provider N = 24 Practice N = NR	Specialty: Pediatrics Number of years in practice: NR Type of clinic: Private practices and hospital-based outpatient clinic Geographical region: Southwest Attica (Athens, Greece) Population served: Children	Time of year: December 1, 2005 to June 15, 2006 and September 15, 2006 to June 15, 2007 Patterns of disease activity: NR Locally tailored: NR System level characteristics: NR	NR
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)			
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)		
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)		
Maltezou, 2008 Greece Patient N = 820 Provider N = 24 Practice N = NR	Group A (control) vs. Group B vs. Group C Total Prescription of Antibiotics (% of total patients): 72.2 vs. 33.7 vs. 19.8, p=0.004 Stepwise increase of antibiotic prescriptions in patients with one, two, three, or four clinical criteria: 16.1%, 45.4%, 63.5%, 68.7%, respectively (p<0.001)	Antibiotic resistance: 36.5% of throat swab cultures were resistant to macrolides
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)		
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)		
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)		
Maltezou, 2008 Greece Patient N = 820 Provider N = 24 Practice N = NR	NR	NR
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)		
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)			
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)			
Maltezou, 2008 Greece Patient N = 820 Provider N = 24 Practice N = NR	NR	NR	
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)			
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
McGinn, 2013 United States Patient N = 1,172 Provider N = 168 Practice N = NR	Complaints and diagnoses associated with pharyngitis (sore throat, throat discomfort, streptococcal pharyngitis) or pneumonia (possible pneumonia, "chest hurts when breathing")	Attendings, residents, fellows, and nurse practitioners working in the outpatient primary care clinic	Type: Clinical and System-level Target: Providers Description: Clinical prediction rules: Walsh and Heckerling; EHR integrated. Risk score calculator that produced management recommendations; 1-hr, in-person training on CPRs, the evidence supporting the CPRs, tool demonstration, patient encounter simulation video; CPR tool triggered by complaints and diagnoses associated with pharyngitis or pneumonia or a diagnosis and test order combination; score of 0-1 indicated intermediate likelihood of streptococcal pharyngitis and recommendation was to obtain a throat swab or symptom resolution; score of 2 or higher was to start antibiotics. Validity/reliability not reported.
McIsaac, 2002 Canada Patient N = 621 children and adults with sore throat Provider N = 97 family practice MDs Practice N = NR	Acute sore throat age 3 years or older. Patients with prior antibiotics in last week or immunocompromised were excluded. Physicians asked to enroll 8 patients meeting these criteria. No other systematic enrollment advice/rules used	A sample of Ontario family physicians invited to participate who had prior participation in practice-based research projects as well as random sample from family physician of Canada general membership. Among these, MDs were randomized to intervention versus control	Type: System-level Target: Providers Description: Clinical decision tool/educational material sent to providers (pharyngitis symptom check list that is used to guide use of antibiotics). Unclear if this tool is validated and even correlates with need for antibiotics.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
McGinn, 2013 United States Patient N = 1,172 Provider N = 168 Practice N = NR	Usual care plus background information on Walsh and Heckerling CPRs	NR	Mean Age: 46 % female: 23.4 Ethnicity: 30% white, 19% black, 12% Hispanic, 39% other SES: NR Educational level: NR Frailty: NA Comorbidities: 17% asthma, 2% COPD, 14% diabetes, 3% CHF Prior RTIs: NR Prior use of antibiotics: NR
McIsaac, 2002 Canada Patient N = 621 children and adults with sore throat Provider N = 97 family practice MDs Practice N = NR	Participating physicians who did not receive tool/education	Patient characteristics: sore throat Type of RTI: pharyngitis Types of Signs and Symptoms: sore throat Duration of Signs and Symptoms: not defined When counting started for duration: not defined	Patient characteristics Mean Age: 28 years % female: 65-69% Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: excluded in last week. Otherwise NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
McGinn, 2013 United States Patient N = 1,172 Provider N = 168 Practice N = NR	Specialty: Mix Number of years in practice: Mix Type of clinic: 2 large urban ambulatory primary care practices at Mount Sinai Medical Center Geographical region: New York Population served: racially/ethnically diverse; almost 56%of patients self-identifying as Hispanic, 35% as African American, 7% as white, and 2% as other races/ ethnicities	Time of year: 11/2010-10/2011 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Academic medical center	NR
McIsaac, 2002 Canada Patient N = 621 children and adults with sore throat Provider N = 97 family practice MDs Practice N = NR	Provider characteristics: N=164 randomized, but only 97 (59%) completed study. Used MV logistic to adjust for differences between control and intervention groups Specialty: family practice Number of years in practice: 22.8% of control >20 years, and 30% of intervention > 20 years practice Type of clinic: Family practice outpatient. Solo practice 20% versus 34% control versus intervention Geographical region: Ontario Population served: general	NR	"unnecessary antibiotics" defined as when antibiotics given and subsequent throat culture was negative.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
McGinn, 2013 United States Patient N = 1,172 Provider N = 168 Practice N = NR	Antibiotic orders at POC (N=1172): 29.2% vs. 38.4%; age-adjusted RR=0.74; 95% CI, 0.6 to 0.92 Antibiotic orders at 2 weeks after CPR visit (N=984): 12.5% vs. 40%; p=0.45	NR
McIsaac, 2002 Canada Patient N = 621 children and adults with sore throat Provider N = 97 family practice MDs Practice N = NR	Unnecessary antibiotic rate compared between groups 16% of patients in control group versus 20.4% in intervention. After adjusting for differences between groups, intervention group was less likely to give unnecessary antibiotics OR=0.76; 95% CI, 0.42 to 1.4 and overall antibiotic use OR=0.57; 95% CI, 0.27 to 1.17. Note neither OR reached statistical significance	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
McGinn, 2013 United States Patient N = 1,172 Provider N = 168 Practice N = NR	NR	ED visits: 0.7% vs. 0.5%; p=0.99 Outpatient clinic visits: 7.7% vs. 11.3%; p=0.10
McIsaac, 2002 Canada Patient N = 621 children and adults with sore throat Provider N = 97 family practice MDs Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
McGinn, 2013 United States Patient N = 1,172 Provider N = 168 Practice N = NR	NR	Chest radiograph order: 21.2% vs. 20.7%; age-adjusted RR=0.98; 95% CI, 0.60 to 1.62	
McIsaac, 2002 Canada Patient N = 621 children and adults with sore throat Provider N = 97 family practice MDs Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Meeker, 2014 United States Patient N= 954 Provider N = 14 Practice N = 5	18 years old or older who experienced a visit encounter with a study clinician involving an ARI diagnosis for which antibiotics might or might not have been appropriate	Medical professionals licensed to prescribe medications (including antibiotics) and who treated adults patients (≥ 18 years)	Type: Educational Target: Providers Description: Study tested "nudges" influence on decision making with regard to judicious use of antibiotics. Intervention consisted of displaying large poster-sized commitment letters in examination rooms for 12 weeks. The letters, featuring clinician photographs and signatures, stated their commitment to avoid inappropriate antibiotics prescribing for ARIs.
Metlay, 2007 United States Patient N = 5,500 Provider N = NR Practice N = 16 VA and non-VA hospital Emergency Departments	Adults (> 18 years) with ICD-9 codes for acute RTIs	Emergency department physicians	Type: Education Target: Patients and Providers Description: Clinical leaders at each ED site were identified and trained on the principles of judicious antibiotic use, using slide sets and published manuscripts. These leaders then conducted one-on-one, and small or large group education sessions at their own sites during the month prior to data collection. Clinicians were also given site-specific data on their use of antibiotics for Acute RTIs with benchmarking to other sites and evidence-based guidelines. Materials targeted at patients included waiting room posters and brochures from the CDC Get Smart program displayed in waiting rooms, and an interaction video kiosk with information specific to acute RTI in waiting rooms, and posters in exam rooms supporting evidence.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Meeker, 2014 United States Patient N= 954 Provider N = 14 Practice N = 5	No poster intervention group (control)	Type of RTI: ARI Types of signs and symptoms: NR Duration of signs and symptoms: NR When counting started for duration: NR	Mean Age: 48.4 years % female: 77.4% Ethnicity: NR SES: 43.1% insured Educational status: NR Frailty: NR Comorbidities: NR Prior RTIs: NR
Metlay, 2007 United States Patient N = 5,500 Provider N = NR Practice N = 16 VA and non-VA hospital Emergency Departments	No intervention	Types of RTI: Nonspecific RTI 34%, Acute bronchitis 23%, Pharyngitis 13%, Other Acute RTI 13% Other characteristics: NR	Age: 18-44 (43%), 45-64 (38%), >65 (19%) % female: 32% Comorbidities: Chronic lung disease (9%), Diabetes (15%), Asthma (11%) Prior RTI: 9% Other characteristics: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Meeker, 2014 United States Patient N= 954 Provider N = 14 Practice N = 5	Specialty: NR (11 physicians and 3 nurse practitioners) Number of years in practice: 17.64 (mean years since licensure) Type of clinic: Community clinics Population served: NR	Time of year: Randomization in February 2012, intervention lasted 12 weeks Patterns of disease activity: Study conducted during a complete 1-year flu cycle Locally tailored: NR System-level characteristics: NR	Appropriateness of antibiotics based on ICD-9 ARI diagnosis codes
Metlay, 2007 United States Patient N = 5,500 Provider N = NR Practice N = 16 VA and non-VA hospital Emergency Departments	Attending alone or with house staff: 89% RN/PA/NP: 11% 50% VA/50% non-VA EDs in metropolitan areas Geographical region: 2 sites from each of 4 US regions	Time of Year: November - February	Nonappropriate: acute upper respiratory tract infection and acute bronchitis. Appropriate: community-acquired pneumonia, sinusitis, acute exacerbations of chronic bronchitis, otitis media and pharyngitis

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Meeker, 2014 United States Patient N= 954 Provider N = 14 Practice N = 5	Poster Condition vs. Control Condition Adjusted* rates of Inappropriate Antibiotic Prescribing, %: Baseline: 43.5; 95% CI, 38.5 to 49.0 vs. 42.8; 95% CI, 38.1 to 48.1 Final Measurement: 33.7; 95% CI, 25.1 to 43.1 vs. 52.7; 95% CI, 44.2 to 61.9 Absolute % change: -9.8; 95% CI, 0.0 to -19.3 vs. 9.9; 95% CI, 0.0 to 20.2 Difference in differences between poster and control conditions: -19.7; 95% CI, -5.8 to -33.04; p=0.02 Inappropriate prescribing rates by group during intervention period, Poster condition vs. Control condition: 36.0% vs. 48.8%; Difference: 12.8%	NR
Metlay, 2007 United States Patient N = 5,500 Provider N = NR Practice N = 16 VA and non-VA hospital Emergency Departments	Intervention vs. Control Combined Acute RTI or acute bronchitis: Intervention groups: -10%; 95% CI, -18% to -2% Control groups: -0.5%; 95% CI, -3% to +5% Acute RTI: -9.5% vs -0.3% (no variance reported) Acute bronchitis -5.0% vs -5.7% (no variance reported) No interaction between VA and non-VA sites.	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Meeker, 2014 United States Patient N= 954 Provider N = 14 Practice N = 5	NR	NR
Metlay, 2007 United States Patient N = 5,500 Provider N = NR Practice N = 16 VA and non-VA hospital Emergency Departments	Intervention vs. Control Subsequent hospitalization -1.8 vs. -1.5; p=0.51	Intervention vs. Control Returns to ED for followup care: +1% vs. +5%; p=0.48 Patient satisfaction +0.2 in both groups; p=0.71

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Meeker, 2014 United States Patient N= 954 Provider N = 14 Practice N = 5	NR	NR	*Adjusted for demographic characteristics and insurance status.
Metlay, 2007 United States Patient N = 5,500 Provider N = NR Practice N = 16 VA and non-VA hospital Emergency Departments	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Milos, 2013 Sweden Patient N = NR Provider N = 162 Practice N = 19	URTIs of the following types: common cold, pharyngitis, tonsillitis, acute otitis media, sinusitis, and laryngitis.	Primary care physicians	Type: Communication Target: Providers Description: Two interventions based on behavioral theories - persuasive communication intervention (PCI) and graded task intervention (GTI). All participants (including control) received questionnaire assessing attitudes, beliefs, subjective norms, behavioral intention, perceived behavioral control, risk perception, self-efficacy, anticipated consequences, evidence of habits, and prior planning. GTI intervention included a set of questions and second part asking GP to describe a difficult situation of managing a patient with URTI without prescribing antibiotics and how to handle it. Also used graded task behavior change techniques: rehearsal and action planning (social cognitive theory - SCT). PCI intervention aimed at influencing the GP's belief about the positive consequences of managing URTIs without prescribing an antibiotic. The skill aquisition approach as a training method and therefore an intervention was based on the questionnaires.
Moore, 2009 Little, 2005 United Kingdom Patient N = 807 (562 analyzed) children N= 136 (<16 y) older N= 133 (>60 y) Provider N = 37 Practice N = NR	>3 y, previous well patients with uncomplicated acute illness (≤ 21 days) presenting in primary care with cough as the main symptom and at least 1 symptom or sign localizing to lower tract (sputum, chest pain, dyspnea, wheeze) = LRTI	37 family physicians in the Wessex region of the UK	Type: Multifaceted - Educational Target: Patients Description: A 1 page leaflet about natural history of LRTI, patients' major worries, advice about when to seek further help - Clinical Target: Patients Description: Advice to delay antibiotics-- antibiotics available on request if symptoms not resolved after 14 days

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Milos, 2013 Sweden Patient N = NR Provider N = 162 Practice N = 19	PCI (8 centers) and GTI (7 centers) vs. control (7 centers)	Type of RTI: common cold, pharyngitis, tonsillitis, acute otitis media, sinusitis, and laryngitis Types of Signs and Symptoms: NR Duration of symptoms: NR When counting started for duration: NR	NR
Moore, 2009 Little, 2005 United Kingdom Patient N = 807 (562 analyzed) children N= 136 (<16 y) older N= 133 (>60 y) Provider N = 37 Practice N = NR	1) Leaflet vs. no leaflet 2) Antibiotic groups: a) immediate; b) no offer; c) delayed antibiotics - on request if symptoms not resolved after 10 days	Type of RTI: Lower RTI Types of Signs and Symptoms: Cough, sputum, chest pain, dyspnea, wheeze Duration of Signs and Symptoms: < 21 days When counting started for duration: Cough at presentation	Mean Age: 38-39 % female: NR Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: cough in past 2 years Prior use of antibiotics: prior use in past 2 years (Moore)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Milos, 2013 Sweden Patient N = NR Provider N = 162 Practice N = 19	Specialty: general practice Number of years in practice: <10 years - 41.4% (control), 52.4% (GTI), 35.3% (PCI) 10-20 years - 34.5% (control), 23.8% (GTI), 35.3% (PCI) >20 years - 24.1% (control), 23.8% (GTI), 41.2% (PCI) Type of clinic: public primary health care centers in southern Sweden Population served: NR	Time of year: 1 December 2011 to 15 February 2012 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: public primary care centers	NR
Moore, 2009 Little, 2005 United Kingdom Patient N = 807 (562 analyzed) children N= 136 (<16 y) older N= 133 (>60 y) Provider N = 37 Practice N = NR	Specialty: Family physicians Number of years in practice: NR Type of clinic: Primary care practice Geographical region: UK Population served: General population	Time of year: August 1998 to July 2003 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: National Health Service	Use of antibiotics 14 days after the onset of cough if symptoms continue

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Milos, 2013 Sweden Patient N = NR Provider N = 162 Practice N = 19	Antibiotic prescription rate for all ages, % before/after intervention: 74%/82% (control) vs. 79%/80 (GTI) vs. 79%/78% (PCI) Antibiotic prescription rate for ages 0-6, % before/after intervention: 23/25% (control) vs. 14%/16% (GTI) vs. 14%/12% (PCI) ANOVA test showed significance in 0-6 years PCI group compared with control (P=0.037)	NR
Moore, 2009 Little, 2005 United Kingdom Patient N = 807 (562 analyzed) children N= 136 (<16 y) older N= 133 (>60 y) Provider N = 37 Practice N = NR	(Little) Use of antibiotics by intervention: No/Total # of patients (%), p No leaflet: 160/281 (57) v Leaflet : 159/291 (55). p=0.58 No antibiotics: 28-182 (16), Delayed antibiotics: 39/197 (20), Immediate antibiotics 185-193 (96), p <0.001	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Milos, 2013 Sweden Patient N = NR Provider N = 162 Practice N = 19	NR	NR
Moore, 2009 Little, 2005 United Kingdom Patient N = 807 (562 analyzed) children N= 136 (<16 y) older N= 133 (>60 y) Provider N = 37 Practice N = NR	NR	(Little) Return clinic visits (reattendance in 1 month) fewer reattendances with delayed and immediate: No antibiotics 0.19, delayed 0.12, immediate 0.11; LR test P=0.04 Increased attendance for Leaflet 0.17 vs no leaflet 0.11; LR P=0.02 (Moore) Table 4: Rate of reconsultation with cough based on current and past prescribing, adjust IRR; 95% CI; p leaflet vs no leaflet IRR=1.27; 95% CI, 0.86 to 1.87; p=0.229 Prior antibiotic vs no prior antibiotic IRR=2.55; 95% CI, 1.62 to 4.01; p<0.001

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Milos, 2013 Sweden Patient N = NR Provider N = 162 Practice N = 19	NR	NR	
Moore, 2009 Little, 2005 United Kingdom Patient N = 807 (562 analyzed) children N= 136 (<16 y) older N= 133 (>60 y) Provider N = 37 Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Ozkaya, 2009 Turkey Patient N = 97 Provider N = NR Practice N = NR	Patients aged 3-14 years presenting with influenza like illness admitted to the pediatric emergency department of an urban children's teaching hospital	NR	Type: Clinical - POC: Rapid Influenza Target: Providers Description: Intervention group included patients who were considered to have an influenza-like illness (ILI) but were asked for rapid diagnostic testing for influenza before prescription and further laboratory procedures. Diagnosis of ILI made by the following criteria: fever > 37.8 C for last 48 hours, presence of at least one systemic finding (e.g. myalgia, headache, tiredness), presence of one or more respiratory tract symptoms (e.g. cough, rhinorrhea). Nasopharyngeal specimens were collected using swab and were tested using Influenza A/B rapid test kits.
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)			
Poehling, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Ozkaya, 2009 Turkey Patient N = 97 Provider N = NR Practice N = NR	Control (patients who were prescribed antibiotics without further laboratory investigation in terms of etiology of the fever)	Type of RTI: Influenza A/B Types of symptoms: Myalgia (47.4%), cough (64.9%), rhinorrhea (84.5%), tiredness (59.8%), headache (62.9%) Duration of Signs and Symptoms: 18 (beginning of the symptoms, mean (h)) When counting started for duration: NR	Mean Age: 5.0 % Female: 44.3% Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)			
Poehling, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Ozkaya, 2009 Turkey Patient N = 97 Provider N = NR Practice N = NR	Specialty: NR Type of clinic: Urban children's hospital emergency department Geographical region: NR Population served: NR	Time of year: November 2006 to March 2007 Patterns of disease activity: NR Locally tailored: NR System level characteristics: NR	NR
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)			
Poehling, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Ozkaya, 2009 Turkey Patient N = 97 Provider N = NR Practice N = NR	Group 1 (control) vs. Group 2 (rapid influenza testing) Antibiotic Prescription: 100% vs. 68%; $\chi 2 = 15.367$; $p<0.0001$ Use of unnecessary antibiotics and further need for additional laboratory tests seemed to be prevented in 32% (16/50) of Group 2 patients.	NR
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)		
Poehling, 2006 (Please refer to Doan, 2014 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Ozkaya, 2009 Turkey Patient N = 97 Provider N = NR Practice N = NR	NR	NR
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)		
Poehling, 2006 (Please refer to Doan, 2014 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Ozkaya, 2009 Turkey Patient N = 97 Provider N = NR Practice N = NR	NR	NR	% Positive rapid test result, no rapid testing (Group 1) vs. rapid testing (Group 2): 36 vs. 32; p=NS
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)			
Poehling, 2006 (Please refer to Doan, 2014 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Pontes, 2005 United States Patient N = 105 Provider N = NR Practice N = NR	Young adults (upper-division undergraduate students) attending a university in the Mid-Atlantic region of the US	NR	Type: Educational Target: Patients Description: Participants in the intervention group were given the CDC brochure "A New Threat to Your Health: Antibiotic Resistance" and were also presented with a booklet that contained five sections: (1) context of the study and instructions for participants, (2) a medical case of a patient who had acute, uncomplicated URI and visited a physician on Day 3 for an antibiotic prescription and three physician's opinions about how they would treat the patient (Physician 1 - immediate antibiotic prescription on Day 3, Physician 2 - delayed prescription on Day 3, fill prescription by Day 10, Physician 3 - no prescription written on Day 3, would consider writing prescription by Day 10), (3) information from the CDC brochure in the CDC brochure condition, (4) questionnaire with a series of Likert-scale items anchored by the endpoints 1 and 7, (5) questions about whether information about a physician's antibiotic prescription behavior (a) is helpful for the choice of a primary care physician and (b) should be available to all students.
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)			
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Pontes, 2005 United States Patient N = 105 Provider N = NR Practice N = NR	No antibiotic education (control)	Type of RTI: Simple acute respiratory infections Types of Signs and Symptoms: NR Duration of signs and symptoms: NR When counting started for duration: NR	Mean Age: NR % female: NR Ethnicity: NR SES: NR Educational level: Current upper-division undergraduate students at time of study Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)			
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Pontes, 2005 United States Patient N = 105 Provider N = NR Practice N = NR	Specialty: NR Number of years in practice: NR Type of clinic: NR Geographical region: Mid-Atlantic region of US Population served: University students	Time of Year: NR Patterns of disease activity: NR Locally tailored: Yes System level characteristics: NR	Appropriate antibiotic use outlined in CDC brochure "A New Threat to Your Health: Antibiotic Resistance"
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)			
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Pontes, 2005 United States Patient N = 105 Provider N = NR Practice N = NR	NR	NR
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)		
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Pontes, 2005 United States Patient N = 105 Provider N = NR Practice N = NR	NR	NR
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)		
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)		

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Pontes, 2005 United States Patient N = 105 Provider N = NR Practice N = NR	CDC Brochure Group vs. No Education Group Respondents' choice of day after URI onset to commence antibiotic treatment, mean (SD); p: 3.9 (2.5) vs. 2.4 (2.0); p<0.01 % of respondents who wished to start a course of antibiotics by: Day 3: 57 vs. 82 Day 5: 72 vs. 91 Effect of patient education on respondents' preference of the physicians, mean score (SD); p: Physician 3 (no prescription on Day 3): 4.84 (2.04) vs. 2.84 (1.85); p<0.01 Physician 2 (deferred prescription on Day 3): 3.99 (1.79) vs. 4.38 (1.77); NS Physician 1 (prescription on Day 3): 2.96 (1.73) vs. 5.21 (1.71); p<0.01 Effect of patient education on differences in respondents' ratings of physicians (intervention mean score (SD); p vs. control mean score (SD); p: Physician 3 - Physician 1 Preference: 1.88 (3.35); p<0.05 vs. -2.37 (2.77); p<0.01 Physician 3 - Physician 2 Preference: 0.85 (3.27); NS vs. -1.54 (2.88); p<0.01	NR	
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)			
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)			
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)			
Samore, 2005 United States Patient N = 407,460 community inhabitants (12 rural communities) Provider N = 334 primary care clinicians Practice N = NR	Communities in Utah and Idaho containing at least 1 primary care clinic and inpatient facility; population <100 thousand, cities <50 thousand.	Primary care clinicians: emergency department clinicians, family practice, internists, pediatricians, nurse practitioners and Pas	Type: Multifaceted - Educational Target: Community intervention Description: Meetings with community leaders, news releases in print media, distribution of educational materials at pharmacies and MD offices, and mailing to parents of children <6 y. Message: "do not treat viral infections with antibiotics" - System level Target: Providers Description: CDSS = clinical decision support system, a direct intervention with primary care providers, using a PDA-based CDSS generated diagnostic and therapeutic recommendation on the basis of patient specific information that was input about the suspected diagnosis. Therapeutic recommendations included OTC medications for symptom control and prescription antimicrobials. Feedback given about prescribing data from the first year at the community level.
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)			
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)			
Samore, 2005 United States Patient N = 407,460 community inhabitants (12 rural communities) Provider N = 334 primary care clinicians Practice N = NR	Community intervention alone vs. intervention plus CDSS targeted toward primary care providers	Type of RTI: Pharyngitis, OM, bronchitis, upper respiratory tract infection, sinusitis, pneumonia, croup, influenza Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: Visit documented in chart for acute RTI	Mean Age: NR % female: 49-51% (69-72% adults) Ethnicity: Non-Hispanic white 85-93% SES: median household income 33,3 thousand-36,3 thousand Educational level: 50-58% college educated Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: 72-84 prescriptions/100 person-years
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)			
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)			
Samore, 2005 United States Patient N = 407,460 community inhabitants (12 rural communities) Provider N = 334 primary care clinicians Practice N = NR	Specialty: General practice Number of years in practice: NR Type of clinic: city practice, group practice, specialist practice Geographical region: The Netherlands Population served: General population	Time of year: January 2002 to September 2003 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Rural communities, community clinics	Based on diagnostic categories of RTI 1) never indicated (acute bronchitis, colds, upper RTI); 2) sometimes indicated (sinusitis and uncharacterized otitis media or pharyngitis); 3) always indicated (strep pharyngitis, acute otitis media, pneumonia)
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)		
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)		
Samore, 2005 United States Patient N = 407,460 community inhabitants (12 rural communities) Provider N = 334 primary care clinicians Practice N = NR	Observed antimicrobial prescribing rates by study arm and year Total prescriptions: mean difference in prescribing rate; 95% CI; p CDSS: first intervention year vs. baseline: -1.1; 95% CI, -4.3 to 2.2; NS second year vs. baseline: -8.8; 95% CI, -13.2 to -4.2 Community intervention alone first intervention year vs. baseline: 2.5; 95% CI, -2.0 to 7.2; NS second year vs. baseline: 0.9; 95% CI, -6.2 to 8.5 Nonstudy communities first intervention year vs. baseline: -2.5; 95% CI, -6.7 to 2.0 second year vs. baseline: 2.6; 95% CI, -3.7 to 9.4 Relative change in prescribing rates: CDSS: first intervention year vs. baseline: -1%, NS second year vs. baseline: -10%; p=.03 Community intervention alone first intervention year vs. baseline: +3%, NS second year vs. baseline: +1% Nonstudy communities first intervention year vs. baseline:-3%, NS second year vs. baseline: +6% Analysis (Figure 2) Relative change in prescribing for "never indicated" aka appropriateness/ relative risk reduction CDSS vs. CI only: 32% vs. 5%; p=0.03	NR
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)		
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)		
Samore, 2005 United States Patient N = 407,460 community inhabitants (12 rural communities) Provider N = 334 primary care clinicians Practice N = NR	NR	NR
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)			
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)			
Samore, 2005 United States Patient N = 407,460 community inhabitants (12 rural communities) Provider N = 334 primary care clinicians Practice N = NR	NR	NR	
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			
Sondergaard, 2003 Denmark Patient N = 455,843 Provider N = 299 Practice N = NR	Patients with respiratory tract infections	GPs in primary care practices (solo and partnership)	Type: Multifaceted: Educational and System-level Target: Providers Description: Intervention group received mailed information about their own prescriptions for antibiotics together with the clinical guideline on the diagnosis and treatment of respiratory tract infections; Feedback included prescription rates for 4 classes of antibiotics (# prescriptions issued/year/100 patients) Key message: to restrict overall consumption of antibiotics used for RTI to the lowest justifiable level, and narrow spectrum penicillins should be preferred to broad spectrum antibiotics.
Spiro, 2004 United States Patient N = 698 (681 with data) Provider N = NR Practice N = 1 pediatric hospital	Children 6 to 35 months of age who presented to a pediatric emergency department with either fever or upper respiratory infection symptoms (e.g. rhinorrhea, cough, or any combination of those findings)	Minimum of 3 years of pediatric residency training	Type: Clinical - POC: Tympanometry Target: Clinicians Description: Tympanometry was performed for all subjects using a single frequency (266-Hz) tympanometer. In Tymp Aware group, printed tympanometry results and tympanometry interpretive guide were provided to the attending physician for analysis and used in patient care. All tympanometry curves were graded by an investigator who was blinded to the final diagnosis.
Spiro, 2006 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			
Sondergaard, 2003 Denmark Patient N = 455,843 Provider N = 299 Practice N = NR	Clinical guidelines (45 page booklet) plus postal feedback versus guidelines alone	Patient characteristics: Type of RTI: acute tonsillitis, acute otitis media, acute sinusitis, asthmatic bronchitis in children, acute exacerbation of COPD and pneumonia Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Mean Age: NR % female: 50.8% Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Spiro, 2004 United States Patient N = 698 (681 with data) Provider N = NR Practice N = 1 pediatric hospital	Tymp Unaware (control), in which attending physician was blinded to the tympanometry results	Type of RTI: Acute OM (26.3%), serous OM (4.6%) Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Mean Age: 17.25 months % female: 43.0% Ethnicity: Black (76.2%), White (17.6%), Hispanic (5.0%), Other (1.2%) SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR
Spiro, 2006 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Provider Characteristics: Specialty Number of Years in Practice Type of Clinic Geographical Region Population Served	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			
Sondergaard, 2003 Denmark Patient N = 455,843 Provider N = 299 Practice N = NR	Specialty: GPs Number of years in practice: NR Type of clinic: solo and partnership practices, primary care/ family practice Geographical region: Denmark Population served: general population (National health service)	Time of year: 7/1997-7/1998 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: National health service	NR
Spiro, 2004 United States Patient N = 698 (681 with data) Provider N = NR Practice N = 1 pediatric hospital	Specialty: Pediatrics (> 3 years of pediatric residency training) Number of years in practice: NR Type of clinic: Pediatric emergency room Geographical region: Alabama Population served: Children	Time of year: May 2001 - August 2002 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: Study conducted at one pediatric hospital in Alabama (Children's Hospital of Alabama)	NR
Spiro, 2006 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		
Sondergaard, 2003 Denmark Patient N = 455,843 Provider N = 299 Practice N = NR	Intervention (I) vs. Control (C) Antibiotic prescription rate before intervention: All antibiotics: 23.5 (16.7; 30.9) vs. 22.3 (17.1; 26.8) Antibiotic prescription rate after intervention: All antibiotics: 34.6 (23.4; 44.8) vs. 34.0 (24.2; 40.8) Fraction of prescriptions for narrow spectrum PCN Before intervention: 0.52 (0.44; 0.62) vs. 0.52 (0.43; 0.62) After: 0.45 (0.39; 0.53) vs. 0.43 (0.34; 0.54) Mean Change: -0.07 (-0.09; -0.05) vs. -0.09 (-0.11; -0.07) Difference in change: 0.02 (-0.01;-0.05)	NR
Spiro, 2004 United States Patient N = 698 (681 with data) Provider N = NR Practice N = 1 pediatric hospital	Tymp Aware vs. Tymp Unaware Antibiotics prescribed for OM (No. (%)) Yes: 98 (28.8) vs. 91 (26.8) No: 243 (71.2) vs. 249 (73.2) p=0.62	NR
Spiro, 2006 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)		
Sondergaard, 2003 Denmark Patient N = 455,843 Provider N = 299 Practice N = NR	NR	NR
Spiro, 2004 United States Patient N = 698 (681 with data) Provider N = NR Practice N = 1 pediatric hospital	NR	NR
Spiro, 2006 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)			
Sondergaard, 2003 Denmark Patient N = 455,843 Provider N = 299 Practice N = NR	NR	NR	
Spiro, 2004 United States Patient N = 698 (681 with data) Provider N = NR Practice N = 1 pediatric hospital	NR	NR	
Spiro, 2006 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Takemura, 2005 Japan Patient N = 305 (301 with data) Provider N = 11 Practice N = NR	New outpatients at Nishi-Ohmiya Hospital presenting with an acutely febrile condition (clinically relevant fever ≥ 37.5 °C) and symptom(s) suspected of infection at the time of (or during the week before) the initial consultation	NR	Type: Clinical - POC: C-Reactive Protein + White Blood Cell Count Target: Clinicians Description: Patients were randomized to advance testing group or non-advance testing group. Patients in the advance testing group underwent CRP and white blood cell (WBC) count testing prior to initial consultation and patient consultation was concurrent with testing process (initial clinical diagnosis and prescribing decisions made after test results were reported). CRP results available in 40-50 minutes and WBC results available in 10 minutes. Between run imprecision ranged from 3.3% to 6.3% at 5-22 mg/L for CRP and from 5.3% to 5.9% at 2.5-6.8 x 109/L for WBC. Reference intervals were ≤ 5 mg/L for CRP and 3.5-9.0 x 109/L for WBC.
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)			
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)			
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)			
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Takemura, 2005 Japan Patient N = 305 (301 with data) Provider N = 11 Practice N = NR	Nonadvance testing group (did not receive tests before the initial consultation [diagnosis and decisionmaking for patient treatment and management made based on patient history and physical examination])	Type of RTI: Acute URI (79.7%), pneumonia/pleuritis (2.3%), influenza (12.6%) Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	NR
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)			
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)			
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)			
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Takemura, 2005 Japan Patient N = 305 (301 with data) Provider N = 11 Practice N = NR	Specialty: General/internal medicine Number of years in practice: 5-29 years of experience in clinical practice Type of clinic: General/internal medicine clinic of Nishi-Ohmiya Hospital (large regional/community hospital) Geographical region: Japan Population served: NR	Time of year: December 2000 - January 2003 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	NR
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)			
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)			
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)			
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Takemura, 2005 Japan Patient N = 305 (301 with data) Provider N = 11 Practice N = NR	Advanced Testing vs. No Advanced Testing % Receiving Antibiotics (Number of Patients Receiving Antibiotics/Number Diagnosed) Acute upper or lower respiratory tract infections: 57.5% (61/106) vs. 91.0% (122/134) Pneumonia/pleuritis: 100% (6/6) vs. 100% (1/1) Influenza: 18.5% (5/27) vs. 36.4% (4/11) Total (including non-ARI diagnoses): 46.6% (76*/163) vs. 78.5% (135*/172) Patients prescribed oral and/or parental antibiotics at reconsultation: 5 vs. 9 (p=0.11)	NR
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)		
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)		
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)		
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Takemura, 2005 Japan Patient N = 305 (301 with data) Provider N = 11 Practice N = NR	Advanced Testing vs. No Advanced Testing Hospital admission at reconsultation: 1 vs. 0 (p=NR)	NR
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)		
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)		
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)		
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Takemura, 2005 Japan Patient N = 305 (301 with data) Provider N = 11 Practice N = NR	NR	NR	*p<0.001 for difference between the two patient groups
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)			
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)			
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)			
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
van Driel, 2007 Belgium Patient N = 408 Provider N = 75 Practice N = NR	Patients with rhinosinusitis according to definition in a newly published guideline.	Providers participating in Quality Circles (part of national accreditation since 1996; consists of 8-25 members practicing in local area who meet at least four times a year). Groups that participated in the development and validation of the guideline were excluded	Type: Education Target: Providers Description: Quality circles dedicated one meeting to discussion of the new guideline on rational use of antibiotics to treat rhinosinusitis. The guideline had been mailed to all GPs prior to the intervention. During the meeting a researcher trained in academic detailing led the discussion, using a review of the evidence, flowcharts, patient expectations, patient pamphlets and case vignettes.
Welschen, 2004 The Netherlands Patient N = 3,620 Provider N = 89 GPs Practice N = 12 groups	Patients with respiratory tract infections	12 peer review groups of GPs and their collaborating pharmacies in the Netherlands	Type: Multifaceted Target: Providers and patients Description: Educational component aimed at providers (group education), assistants of GPs and pharmacists (group education), and patients (educational material). Monitoring/feedback on prescribing behavior.
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)			
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
van Driel, 2007 Belgium Patient N = 408 Provider N = 75 Practice N = NR	Control group quality circles were asked to schedule a meeting about the guideline but without academic detailing	Type of RTI: Rhinosinusitis Types of Signs and Symptoms: Purulent nasal secretions (41%), 2-phased illness (52%), fever (22%) Duration of Signs and Symptoms: Mean duration 5 days When counting started for duration: Unclear	Mean Age: 38 y % female: 61% Comorbidities: 30% with recurrent acute rhinosinusitis All other characteristics: NR
Welschen, 2004 The Netherlands Patient N = 3,620 Provider N = 89 GPs Practice N = 12 groups	Group education, monitoring of prescribing behavior, education of assistants/pharmacists, educational materials for patients vs. None	Patient characteristics: Type of RTI: any acute symptoms of the respiratory tract Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Intervention versus Control Mean Age: 29-31 vs. 29-30 % female: 52-54% vs. 54-55% Ethnicity: NA SES: NR Educational level: NR Frailty: NR Comorbidities: Asthma (6.7-8.2% vs. 5.4-7.2%), Prior RTIs: NR Prior use of antibiotics: NR
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)			
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
van Driel, 2007 Belgium Patient N = 408 Provider N = 75 Practice N = NR	Specialty: 66% general practitioners Number of years in practice: 20 y (mean) All other characteristics: NR	NR	NR (per guideline) "antibiotics are generally not needed to treat this condition"
Welschen, 2004 The Netherlands Patient N = 3,620 Provider N = 89 GPs Practice N = 12 groups	Specialty: GPs Number of years in practice: 12 vs. 15 Type of clinic: single 19 vs. 28; group 81 vs. 72 Geographical region: Netherlands Population served: general population (national health service)	Time of year: 3 weeks in autumn and winter Patterns of disease activity: NR Locally tailored: yes System-level characteristics: single vs. group; national health service	Prescribed if indicated by evidence based guidelines
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)			
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
van Driel, 2007 Belgium Patient N = 408 Provider N = 75 Practice N = NR	Antibiotics prescribed: Adjusted OR=0.63; 95% CI, 0.29 to 1.37 Intervention 56.9% vs. control 58.3%	NR
Welschen, 2004 The Netherlands Patient N = 3,620 Provider N = 89 GPs Practice N = 12 groups	Intervention(n=42) vs. controls (n=47), # (%) antibiotics prescription rates in 2000 (pre) and 2001 (post), % change (SD) 27 (16.9), 23 (15.6); -4 (15.6) vs. 29 (16.6), 37 (18.1); +8 (19.2); Mean difference of changes: -12; 95% CI, -18.9 to - 4.0 -10.7; 95% CI, -20.3 to -1.0 Changes in mean number of antibiotic prescriptions per 1000 patients in March-April-May 2000 vs. 2001 (Intervention versus Control) 76.4 (28.1), 66.7 (25.9); -9.7 (19.8) vs. 85.4 (31.7), 87.4 (24.0); +1.9 (19.3) Mean difference: -12; 95% CI, -23.3 to -0.03 Intervention group had decrease by 9.7 RX/ 1000 patients (p=0.05) vs. increase of 1.9/1000 (p=0.6)	NR
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)		
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
van Driel, 2007 Belgium Patient N = 408 Provider N = 75 Practice N = NR	NR	NR
Welschen, 2004 The Netherlands Patient N = 3,620 Provider N = 89 GPs Practice N = 12 groups	NR	Patient satisfaction reported as % change (Table 3) 2000 (pre) and 2001 (post), % change (SD) 4.3 (0.3), 4.3) (0.3); 0 (0.4) vs 4.2 (0.4), 4.2 (0.3); 0 (0.4): No difference
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)		
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
van Driel, 2007 Belgium Patient N = 408 Provider N = 75 Practice N = NR	NR	NR	
Welschen, 2004 The Netherlands Patient N = 3,620 Provider N = 89 GPs Practice N = 12 groups	NR	NR	
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)			
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-Level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Worrall, 2007 Newfoundland Patient N = 533 Provider N = 40 urban and suburban family practitioners (37 entered patients in the trial) Practice N = NR	Adult patients aged 19 years or older who presented with acute sore throat as their primary symptom	Urban and suburban family practitioners	Type: System and Clinical - POC: Rapid Strep Target: Clinicians Description: (1) Sore throat decision rules only (STDR), (2) rapid antigen detection test (RADT), or (3) STDR and RADT. Modified version of STDR based on those developed by Centor et al. at the University of Virginia. Score ≤ 1 suggested no need for antibiotics. Score of 2 suggested antibiotics might or might not be beneficial. Score or 3 or 4 suggested antibiotics were required. In combined STDR/RADT intervention, RADT was used only when score of STDR was 2. RADT used was Clearview(R) Exact Strep A dipstick from Wampole Laboratories (sensitivity ≈ 90%, specificity ≈ 95%).
Worrall, 2010 Newfoundland/Labrador Patient N = 149 Provider N = 8 Practice N = NR	Consecutive adult patients (aged 18 years or older) with acute upper respiratory tract infections for whom the clinicians thought antibiotic treatment might not be necessary	NR	Type: Clinical Target: Patient Description: Postdated prescription

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **Socioeconomic Status** **Educational level** **Frailty** **Comorbidities** **Prior RTIs** **Prior Use of Antibiotics**
Worrall, 2007 Newfoundland Patient N = 533 Provider N = 40 urban and suburban family practitioners (37 entered patients in the trial) Practice N = NR	Control (usual clinical practice)	Type of RTI: Streptococcal sore throat Types of Signs and Symptoms: Sore throat Duration of Signs and Symptoms: NR When counting started for duration: NR	NR
Worrall, 2010 Newfoundland/Labrador Patient N = 149 Provider N = 8 Practice N = NR	Usual prescription	Type of RTI: URTI=30%, sinusitis=20%, bronchitis=17%, pharyngitis=17%, acute otitis media=13%, soft tissue infection=1%, laryngitis=1%, community acquired pneumonia=1% Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**
Worrall, 2007 Newfoundland Patient N = 533 Provider N = 40 urban and suburban family practitioners (37 entered patients in the trial) Practice N = NR	Specialty: Family practice Number of years in practice: 17.4 years (mean no. of years since graduation) Type of clinic: Urban and suburban family practices Geographical region: Eastern Newfoundland Population served: Urban and suburban populations	Time of year: February, March, and April 2005 Patterns of disease activity: NR Locally tailored: NR System-level characteristics: NR	Score ≤ 1 on Centor et al. modified STDR suggested no need for antibiotics. Score of 2 suggested antibiotics might or might not be beneficial. Score or 3 or 4 suggested antibiotics were required.
Worrall, 2010 Newfoundland/Labrador Patient N = 149 Provider N = 8 Practice N = NR	Specialty: Family practice Number of years in practice: NR Type of clinic: NR Geographical region: Small community Population served: NR	Time of year: NR Patterns of disease activity: NR Locally tailored: NA System-level characteristics: Small community	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Worrall, 2007 Newfoundland Patient N = 533 Provider N = 40 urban and suburban family practitioners (37 entered patients in the trial) Practice N = NR	% of Visits Where Antibiotics Were Prescribed Usual Care vs. STDR only vs. RADT only vs. STDR + RADT vs. Total: 58.2 vs. 55.3 vs. 26.7* vs. 38.2* vs. 46.7	NR
Worrall, 2010 Newfoundland/Labrador Patient N = 149 Provider N = 8 Practice N = NR	Filled prescriptions: Postdated=44% vs. usual=43.2%; NS	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Worrall, 2007 Newfoundland Patient N = 533 Provider N = 40 urban and suburban family practitioners (37 entered patients in the trial) Practice N = NR	NR	NR
Worrall, 2010 Newfoundland/Labrador Patient N = 149 Provider N = 8 Practice N = NR	NR	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Worrall, 2007 Newfoundland Patient N = 533 Provider N = 40 urban and suburban family practitioners (37 entered patients in the trial) Practice N = NR	NR	NR	* p < 0.001 for reduction in antibiotic prescribing in RADT only vs. usual care and STDR + RADT vs. usual care groups
Worrall, 2010 Newfoundland/Labrador Patient N = 149 Provider N = 8 Practice N = NR	NR	NR	

Please see Appendix B, Included Studies, for full study references.

Appendix E. Quality Assessment of Randomized Controlled Trials

Quality (Risk of Bias) Assessment of Individual Studies

Determination of Ratings

Studies that had a serious flaw were rated poor in quality, studies that met all criteria were rated good in quality, and the remainder of the studies were rated fair in quality. As the fair quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair quality studies are likely to be valid, while others are only possibly valid. A poor quality study is not valid as the results are at least as likely to reflect flaws in the study design as a true difference between the compared interventions. A serious flaw is reflected by failure to meet combinations of items on the quality assessment checklist; for example, unclear randomization and allocation concealment methods combined with differences between randomized groups at baseline in potentially prognostic characteristics and either high attrition or lack of an intention to treat analysis. Quality assessments of studies included in this review are included in the following evidence tables.

Note Regarding Evidence Table

Quality assessments for each included study are contained in separate rows of the evidence table (included below). Evidence rows for each study span multiple pages of this appendix document. Each study is identified in the first column of the evidence table.

Evidence Table E1. Quality assessment of randomized controlled trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Alder, 2005 (Please refer to Andrews, 2012 systematic review)					
Altiner, 2007	Unclear	Unclear	No	NR	No
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)					
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)					
Baer, 2013	Yes	Yes	Yes	Yes	No
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)					
Bauchner, 2006 (Please refer to Andrews, 2012, Boonacker, 2010, and Vodicka, 2013 systematic reviews)					

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)					
Bonner, 2003 (Please refer to Doan, 2012 systematic review)					
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)					
Briel, 2006	Yes	Yes	Yes	Yes	No
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					
Brittain-Long 2011	No	Yes	Yes	No	No
Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
Alder, 2005 (Please refer to Andrews, 2012 systematic review)					
Altiner, 2007	NR	Yes	No	No	Poor
Anderson, 1980 (Please refer to Andrews, 2012 systematic review)					
Arroll, 2002 (Please refer to Spurling, 2013 systematic review)					
Baer, 2013	Yes	Yes	Yes	Yes	Good
Bauchner, 2001 (Please refer to Andrews, 2012 systematic review)					
Bauchner, 2006 (Please refer to Andrews, 2012, Boonacker, 2010, and Vodicka, 2013 systematic reviews)					
Bennett, 2001 (Please refer to Boonacker, 2010 systematic review)					
Bonner, 2003 (Please refer to Doan, 2012 systematic review)					
Bourgeois, 2010 (Please refer to Vodicka, 2013 systematic review)					
Briel, 2006	NR	Yes	Yes	Yes	Fair
Briel, 2008 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					
Brittain-Long 2011	No	Yes	Yes	Yes	Fair
Burkhardt, 2010 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Cals, 2009 Cals, 2010 Cals, 2011 Cals, 2013	Unclear	Unclear	Unclear, some differences in current smoking and shortness of breath	Unclear	No
Carling, 2009	Yes, used computerized block-randomization	Yes, the system randomized participants upon log on to study Web site	Yes	Unclear	NA, no clinicians involved in study
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)					
Chazan, 2007	Unclear	Unclear	Yes	Unclear	No
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)					
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					
Coenen, 2004	Yes	Yes	Unclear, stated no significant differences in all randomized GPs (N=85), but characteristics not shown; characteristics only shown for subset of GPs who responded both pre- and post-interventions and twice as many GP's had professional training in intervention group; also some between-group differences in patient characteristics	Unclear	No
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)					

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
Cals, 2009 Cals, 2010 Cals, 2011 Cals, 2013	Unclear	No ITT for diary outcomes (e.g. symptoms), 90% completed and returned diaries	Yes	Yes	Fair
Carling, 2009	Unclear, not mentioned	Yes	No, ~56% were randomized but did not complete study	Yes, % that did not complete study was < 10% different for each group	Fair
Chao, 2008 (Please refer to Spurling, 2013 and Andrews, 2012 systematic reviews)					
Chazan, 2007	No	Yes	Yes	Yes	Fair
Christakis, 2001 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)					
Christ-Crain, 2004 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					
Coenen, 2004	Unclear	No, only 693 of 824 included patients were eligible for analysis post-test (84%)	No, only 66% of GP's responded	Yes	Fair (KQ 1) Poor (KQs 2-6)
Cohen, 2000 (Please refer to Vodicka, 2013 systematic review)					

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Croft, 2007 (Please refer to Andrews, 2012 systematic review)					
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)					
Diederichsen, 2000	Yes	No (sealed envelopes)	Clinicians: NA Patients: Yes	Unclear	No (NA)
Doan, 2009 (Please refer to Doan, 2012 systematic review)					
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)					
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)					
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)					
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)					
Finkelstein, 2008	Yes	Unclear	Yes	Unclear	No
Forrest, 2013	Yes	Unclear.	No. Multiple variations at baseline that are discussed in the text and in Tables 2 and 3.	Unclear	Unclear
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)					
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)					
Gerber, 2013	Yes	Unclear	Mostly - Control sites had higher proportion of Black and Medicaid patients	Unclear	No

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
Croft, 2007 (Please refer to Andrews, 2012 systematic review)					
Davis, 2007 (Please refer to Boonacker, 2010 systematic review)					
Diederichsen, 2000	Unclear	Yes	Yes	Yes	Fair
Doan, 2009 (Please refer to Doan, 2012 systematic review)					
Dowell, 2001 (Please refer to Spurling, 2013 systematic review)					
Doyne, 2004 (Please refer to Vodicka, 2013 systematic review)					
El-Daher, 1991 (Please refer to Spurling, 2013 systematic review)					
Finkelstein, 2001 (Please refer to Vodicka, 2013 systematic review)					
Finkelstein, 2008	No	Yes	Yes	Yes	Fair
Forrest, 2013	Unclear	Unclear. Mention of ITT, but unclear how missing data from two practices that withdrew from study were handled.	No. In addition, two practices lost to followup (8%).	Unclear	Poor
Francis, 2009 (Please refer to Vodicka, 2013 and Andrews, 2012 systematic reviews)					
Gerber, 1990 (Please refer to Spurling, 2013 systematic review)					
Gerber, 2013	No	Yes	Yes	Yes (none)	Fair

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Gjelstad, 2013	Unclear	Yes	Unclear, no information on patients	Unclear	Unclear
Gonzales, 2011	Yes	Unclear	Clinicians: NA Patients: Yes	Unclear	No (NA)
Gonzales, 2013	Unclear.	Unclear	Unclear. Some variations at baseline, prognostic influence unclear.	Unclear.	Unclear.
Huang, 2007	Yes, used a computer randomization routine	Unclear, no mention of allocation methods	Yes	Unclear, not mentioned	Unclear, not mentioned
Iyer, 2006 (Please refer to Doan, 2012 systematic review)					
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)					
Légaré, 2010	Yes	Unclear	No	Unclear	No
Légaré, 2012 Légaré, 2013	Yes	Unclear	Yes	Unclear	No
Linder, 2009	Unclear	Unclear	Yes but limited data given	Unclear	No
Linder, 2010	Unclear	Unclear	Yes but limited data given	Unclear	No
Little, 1997 (Please refer to Spurling, 2013 systematic review)					
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic review) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)					
Little, 2013	Yes	Yes	Yes	No	No
Little, 2013 Yardley, 2013	Yes	Unclear	Clinicians: Unclear Patients: Yes	Unclear	No
Little, 2014	Yes	Yes	Clinicians: Unclear Patients: Yes	Unclear	No
Llor, 2011	Yes	Yes	Yes	No	No

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
Gjelstad, 2013	Unclear	No, no followup data from dropouts	Yes	Yes	Fair
Gonzales, 2011	Unclear	Yes	Yes	Yes	Fair
Gonzales, 2013	Unclear.	Unclear. Excluded clinicians who saw <10 patients.	Unclear	Unclear	Fair
Huang, 2007	Unclear, not mentioned	Unclear	Unclear, no data or mention of attrition	Unclear, no data or mention of attrition	Poor
Iyer, 2006 (Please refer to Doan, 2012 systematic review)					
Juzych, 2005 (Please refer to Vodicka, 2013 and Boonacker, 2010 systematic reviews)					
Légaré, 2010	NR	Yes	Yes	Yes	Fair
Légaré, 2012 Légaré, 2013	NR	Yes	Unclear	Unclear	Fair
Linder, 2009	Unclear	Yes	Yes	Yes	Fair
Linder, 2010	Unclear	Yes	Yes	Yes	Fair
Little, 1997 (Please refer to Spurling, 2013 systematic review)					
Little, 2001 (Please refer to Spurling, 2013 and Andrews, 2012 systematic review) Little, 2006 (companion) (Please refer to Spurling, 2013 systematic review)					
Little, 2013	No	Yes	Yes	Yes	Fair
Little, 2013 Yardley, 2013	Unclear	Yes	Yes	Yes	Fair
Little, 2014	No	Yes for reconsultation, no for others (85% for antibiotic use, 24% for satisfaction)	No for satisfaction, yes for others	Yes	Fair
Llor, 2011	No	Yes	Yes	Yes	Fair

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
MacFarlane, 2002	Unclear, randomized by permuted blocks of four but no mention of specific randomization technique/method (e.g. computer)	No, sealed envelope	Yes	Yes	Yes
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)					
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)					
Maltezou, 2008	No	Yes	No	No	No
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic review)					
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)					
McGinn, 2013	Yes	Unclear	Yes, however age was statistically different (p=0.001)	Unclear	Unclear
McIsaac, 2002	Unclear	Unclear	No	Unclear	No
Meeker, 2014	Yes	Unclear	Unclear, some differences in % male patients (25 vs 20), patient age (mean 46 vs 51), insured (48% vs 38%), male MDs (29% vs 14%)	Unclear	No
Metlay, 2007	Yes	Yes	No, some important imbalances: more control sites were VAs (62% vs 50%); slightly more older patients, more smokers, more with previous ARI. Provider types also differed as VAs were teaching hospitals.	Unclear and No, depending on specific outcome	No

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
MacFarlane, 2002	Unclear, not mentioned	Yes, they provide data to calculate this	Yes	Yes	Fair
Maiman, 1988 (Please refer to Boonacker, 2010 systematic review)					
Mainous, 2000 (Please refer to Vodicka, 2013 systematic review)					
Maltezou, 2008	No	Yes	Yes	Yes	Fair
Margolis, 1992 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic review)					
McCormick, 2005 (Please refer to Andrews, 2012 systematic review)					
McGinn, 2013	Unclear	Unclear	Unclear	Unclear	Fair
McIsaac, 2002	Unclear	No	No (41% physician drop-out)	Unclear	Poor
Meeker, 2014	No	Yes	Yes	Yes (none)	Fair
Metlay, 2007	No	No	1 study site discontinued the study (6%)	Yes	Fair

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Milos, 2013	Unclear	Unclear, states allocated blindly but also states consecutive assignment and assignment by practice size.	Unclear, differences in clinician demographics and years of experience.	Unclear	No
Moore, 2009 Little, 2005 (Please refer to Spurling, 2013 systematic review)	Yes	Unclear	Unclear	Unclear	No
Ozkaya, 2009	Unclear	Unclear	Yes	No	No
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)					
Poehling, 2006 (Please refer to Doan, 2012 systematic review)					
Pontes, 2005	Unclear, no mention of randomization of patients to intervention or control arms	Unclear, no mention of allocation methods	Unclear, no mention in text or table with data	Unclear	Unclear
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)					
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)					
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)					
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)					
Samore, 2005	Unclear	Unclear	Yes	Unclear	No
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)					
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
Milos, 2013	Unclear	Unclear	No, 32-46% loss to follow-up	No, 6-14% difference in attrition by group.	Poor
Moore, 2009 Little, 2005 (Please refer to Spurling, 2013 systematic review)	Unclear	No	Yes	No	Fair
Ozkaya, 2009	No	Yes	Yes	Yes	Poor
Pichichero, 1987 (Please refer to Spurling, 2013 systematic review)					
Poehling, 2006 (Please refer to Doan, 2012 systematic review)					
Pontes, 2005	Unclear	Unclear, they do not mention ITT and do not provide the data to calculate this	Unclear, no data or mention of attrition	Unclear, no data or mention of attrition	Poor
Pshetizky, 2003 (Please refer to Andrews, 2012 systematic review)					
Regev-Yochay, 2011 (Please refer to Vodicka, 2013 systematic review)					
Robbins, 2003 (Please refer to Andrews, 2012 systematic review)					
Roberts, 1983 (Please refer to Andrews, 2012 systematic review)					
Samore, 2005	Unclear	Unclear	NR	NR	Fair
Schnellinger, 2010 (Please refer to Andrews, 2012 systematic review)					
Schuetz, 2009 (Please refer to Schuetz, 2011 and Schuetz, 2012 systematic reviews)					

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Sondergaard, 2003	Unclear	Unclear	Unclear, few characteristics reported	No	Unclear
Spiro, 2004	Yes	Unclear	No, there were more males in the unaware group (61.5% vs. 52.5%, p=0.02)	No	No
Spiro, 2006 (Please refer to Andrews, 2012 and Spurling, 2013 systematic reviews)					
Takemura, 2005	Unclear	Unclear	Clinicians: NA Patients: Yes	Unclear	No (NA)
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)					
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)					
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)					
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)					
van Driel, 2007	Unclear, stratification by geographic location but methods not reported	Unclear	Some small differences: more control group clinicians female, solo practice, involved in training program, using HER, and more patients with fever (17.2% vs 26.5%)	Yes	No
Welschen, 2004	Yes	Yes	Yes	Yes	Unclear
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)					
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)					
Worrall, 2007	Unclear	Unclear	Yes for physicians, unclear for patients	Unclear	No

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
Sondergaard, 2003	Unclear	Unclear	Yes	Unclear	Poor
Spiro, 2004	No	Yes	Yes	Yes	Fair
Spiro, 2006 (Please refer to Andrews, 2012 and Spurling, 2013 systematic reviews)					
Takemura, 2005	Unclear	Yes	Yes	Yes	Fair
Taylor, 2003 (Please refer to Andrews, 2012 systematic review)					
Taylor, 2005 (Please refer to Vodicka, 2013 systematic review)					
Thomson, 1999 (Please refer to Andrews, 2012 systematic review)					
Usherwood, 1991 (Please refer to Andrews, 2012 systematic review)					
van Driel, 2007	No but due to cluster randomization, patients may not have known they were even in a study	Yes	Yes	Yes	Fair
Welschen, 2004	Unclear	No, excluded 11%	Yes, 11%	Yes, 9% vs 13%	Fair
Wilson, 2002 (Please refer to Boonacker, 2010 systematic review)					
Wilson, 2003 (Please refer to Vodicka, 2013 systematic review)					
Worrall, 2007	Unclear	Yes	Yes	Yes	Fair

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?
Worrall, 2010	Unclear (NR)	No, blank envelopes, also all clinicians given equal number of usual and postdated and may have guessed remaining as reached end of allotment	Unclear, only reported that range of illnesses were similar, no demographic information	NA	No

Author, Year	Patient or caregiver blinded?	Intention to treat?	Acceptable level of *overall* attrition (20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality (Good, Fair, Poor)
Worrall, 2010	No	Yes	Yes	Yes	Fair

Please see Appendix B, Included Studies, for full study references.

Appendix F. Data Abstraction of Observational Studies

Note Regarding Evidence Table

Data abstractions for each included study are contained in separate rows of the evidence table (included below). Evidence rows for each study span multiple pages of this appendix document. Each study is identified in the first column of the evidence table.

Evidence Table F1. Data abstraction of observational studies

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)				
Bjerrum, 2004 Denmark Patient N = 1,444 Provider N = 367 Practice N = NR	Cross-sectional Patients registered "during a 3-week period (15 working days between 1 November 2001 and 31 January 2002."	Acute sinusitis: provider recorded "suspected focus of infection," and for included patients this was "the paranasal sinuses." No further diagnostic criteria given.	Danish general practitioners (GPs) who used CRP rapid tests. Access to CRP testing was a practice characteristic, suggesting it was availability of test rather than provider choice that defined this group, but selection criteria were not clearly reported. Participating GPs (10% of all Danish GPs) "participated on a voluntary basis" in audit registration.	Type: Clinical - POC: CRP Target: Practice/Provider Description: C-reactive protein (CRP) rapid test. No intervention to promote its use. One GP per practice participated, and access to/use of CRP tests varied by provider/practice.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Bjerrum, 2006 Spain Patient N = 5,250 consultations before and after intervention Provider N = 52 Practice N = NR	Pre/post, with control group for second time period only Patients registered "in a 3-week period during 3 winter months (December to February)" before (2002/2003) and after (2004/2005) intervention.	patients with RTI, no further diagnostic criteria given.	17 general practitioners (GPs) registering patients before (2002/2003) and after (2004/2005) receiving intervention.	Type: Clinical - POC: Multifaceted Target: providers Description: Courses in RTI management following local guidelines, use of two rapid diagnostic tests (rapid strep and CRP).

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)				
Bjerrum, 2004 Denmark Patient N = 1,444 Provider N = 367 Practice N = NR	Danish GPs who did not use CRP rapid tests (see provider population criteria).	Type of RTI: of 17,792 total patients with URIs, 1,444 (8%) had sinusitis and were the focus of the analysis of prescribing outcomes. Signs and symptoms, duration: NR	Patients with sinusitis: Median age: 40 years in CRP practices, 41 years in others % female: 69 overall Other characteristics: NR	All were general practitioners Other characteristics: NR
Bjerrum, 2006 Spain Patient N = 5,250 consultations before and after intervention Provider N = 52 Practice N = NR	35 GPs not exposed to intervention registered patients in 2004/2005	Type of RTI (focus of infection as judged by provider): ears (5.7%), tonsils (5.6%), pharynx/larynx/ trachea (23%), sinuses (2.8%), Bronchi/lungs (31%), diffuse/ multiple foci (28%), unknown/ missing (3.8%) Signs, symptoms and duration: NR	NR	Specialty/type of clinic: general practice Years in practice, population served: NR Geographical region: rural and urban areas of Catalonia, Spain

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)			
Bjerrum, 2004 Denmark Patient N = 1,444 Provider N = 367 Practice N = NR	Time of year: November 1 through January 31 Other factors NR	Not explicitly defined, but background discussion states that symptoms of bacterial and viral sinusitis overlap and that raised CRP can identify bacterial sinusitis, for which antibiotics presumably appropriate. Outcome measured is overall antibiotic prescribing rate for sinusitis.	Logistic regression analysis with antibiotic prescribing rate as a function of access to CRP testing, "adjusted for patient sex, age, number of listed patients and workload in practice" as well as solo vs. group practice.
Bjerrum, 2006 Spain Patient N = 5,250 consultations before and after intervention Provider N = 52 Practice N = NR	Time of year: December to February of two consecutive years Pattern of disease activity, local tailoring, system-level characteristics: NR	Antibiotics for bacterial infections only. "Particularly relevant for reducing antibiotic prescribing are colds, upper RTIs, and bronchitis, because the vast majority of these illnesses have a viral cause and do not benefit from antibiotic treatment." Outcomes reported: overall antibiotic prescribing, prescribing by narrow- vs. broad-spectrum classes.	"we used 95% confidence intervals (CI) adjusted for clustering of data according to practices." Methods not further described. Antibiotic prescribing outcomes also reported stratified by site of infection.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)		
Bjerrum, 2004 Denmark Patient N = 1,444 Provider N = 367 Practice N = NR	Adjusted odds ratio for prescription of antibiotics as a function of access to CRP testing: OR=0.43; 95% CI, 0.33 to 0.58	NR
Bjerrum, 2006 Spain Patient N = 5,250 consultations before and after intervention Provider N = 52 Practice N = NR	Percent (95% CI) of all consultations with antibiotic prescribed: After intervention: 24% (20%-29%) Before intervention: 36% (29%-44%) Control: 32% (27%-38%) Also reported by infection site, with difference most pronounced for sinusitis and lower RTI. Antibiotic type: use of narrow-spectrum penicillin increased after intervention, and use of macrolides and cephalosporins decreased.	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)		
Bjerrum, 2004 Denmark Patient N = 1,444 Provider N = 367 Practice N = NR	NR	NR
Bjerrum, 2006 Spain Patient N = 5,250 consultations before and after intervention Provider N = 52 Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)			
Bjerrum, 2004 Denmark Patient N = 1,444 Provider N = 367 Practice N = NR	NR	NR	
Bjerrum, 2006 Spain Patient N = 5,250 consultations before and after intervention Provider N = 52 Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Bjerrum, 2011 Denmark, Sweden, Lithuania, Russia, Spain, and Argentina Patient N = 47,011 before and after intervention Provider N = 440 Practice N = NR	Pre/post Time frame: patients registered during 3 weeks in the winter months of 2008 and 2009, with intervention "shortly after" first registration.	All patients with RTI, no further diagnostic criteria given.	General practitioners (GPs) registering patients after intervention (2009).	Type: Clinical - POC: Multifaceted Target: providers and patients Description: prescriber feedback; training on antibiotic use; clinical guidelines on RTI management; patient posters, brochures and handouts on antibiotic use; access to and training in Strep A and CRP POC tests.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Bjerrum, 2011 Denmark, Sweden, Lithuania, Russia, Spain, and Argentina Patient N = 47,011 before and after intervention Provider N = 440 Practice N = NR	GPs registering patients before intervention (2008)	Type of RTI: Upper vs. lower reported only in Figure 1 Types of signs and symptoms: NR Duration of signs and symptoms: 3 days (median) When counting started: days before first consultation with GP	Median age: 32 in 2008, 31 in 2009 % female: 57 Other characteristics: NR	Specialty/type of clinic: general practice Years in practice as GP: 15 (median) Population served: NR Geographical region: Denmark, Sweden, Lithuania, Russia, Spain, and Argentina

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Bjerrum, 2011 Denmark, Sweden, Lithuania, Russia, Spain, and Argentina Patient N = 47,011 before and after intervention Provider N = 440 Practice N = NR	Time of year: two consecutive winter seasons Other factors: NR	"The majority of RTIs (90%) are caused by virus and in these cases antibiotics are unlikely to have any clinical benefit...Even if the etiology is bacterial, antibiotics only slightly modify RTIs, particular in patients with upper RTIs." Outcomes reported: antibiotic use for upper and lower RTIs, choice of antibiotic (Penicillin-V, amoxicillin, amoxicillin-clavulanic acid, macrolides, quinolones, tetracycline, cephalosporins).	"we used 95% confidence intervals (CI) adjusted for clustering to GPs." Methods not further described. Antibiotic prescribing outcomes also reported stratified by country.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Bjerrum, 2011 Denmark, Sweden, Lithuania, Russia, Spain, and Argentina Patient N = 47,011 before and after intervention Provider N = 440 Practice N = NR	Change in antibiotic prescribing rate: Lower RTIs: decrease ranged from about 2% (Denmark; estimated from figure) to 42% (95% CI, 36% to 47%; Lithuania) Upper RTIs: decrease ranged from <1% (Denmark; estimated from figure) to 20% (95% CI, 17% to 23%; Lithuania) Change in use of Penicillin-V*: Lower RTIs: ranged from a decrease of 0.9% (Argentina) to an increase of 31.2% (Lithuania) Upper RTIs: ranged from a decrease of 2.2% (Sweden) to an increase of 44.3% (Lithuania) *Use of multiple broad-spectrum antibiotics also reported	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Bjerrum, 2011 Denmark, Sweden, Lithuania, Russia, Spain, and Argentina Patient N = 47,011 before and after intervention Provider N = 440 Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Bjerrum, 2011 Denmark, Sweden, Lithuania, Russia, Spain, and Argentina Patient N = 47,011 before and after intervention Provider N = 440 Practice N = NR	NR	NR	Happy Audit study

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Blaschke, 2014 United States Patient N = 1,166 sampled visits, extrapolated to 4.9 million estimated ED visits Provider N = NR Practice N = NR	Study design: cross-sectional; no intervention, data pooled rather than compared across time, comparison groups defined based on testing and diagnosis with outcomes from concurrent encounter Time frame: three flu seasons (2007-2009).	"We only included visits at which influenza was diagnosed by ICD-9-CM code and/or Rapid influenza diagnostic test (RIDT) was performed." (RIDT test results were not available, only whether test performed.) Adults and children included. 3 groups defined based on "certainty for the diagnosis of influenza," with two groups less likely to have flu: those where RIDT was not performed but flu was diagnosed ("intermediate certainty," RIDT-/INF+); and those where RIDT was performed and flu was not diagnosed ("lowest certainty," RIDT+/INF-).	NR	Type: Clinical - POC: Rapid Influenza Target: provider orders rapid flu test, though no intervention to promote its use Description: Rapid influenza diagnostic test (RIDT). No intervention to promote its use.
Bush, 1979 (Please refer to Boonacker, 2010 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Blaschke, 2014 United States Patient N = 1,166 sampled visits, extrapolated to 4.9 million estimated ED visits Provider N = NR Practice N = NR	Group most likely to have flu was patients with RIDT performed and flu diagnosed ("highest certainty," RIDT+/INF+), and this was used as the reference group.	Type of RTI (primary diagnosis, weighted %): Influenza (20%), acute RTI (43%), unspecified viral infection (9%), fever (9%; listed under diagnoses), other respiratory diagnosis (4%), other diagnosis (15%) Signs and symptoms: temperature ≥ 100.4F (39%, weighted) Duration: NR	Age group: 0-5 (33%), 6-17 (20%), 18+ (47%) % female: 54 Other characteristics: NR	Type of clinic: hospital emergency departments Geographical region/population served: sampling from all 50 US states and DC, but Federal (VA, military) hospitals excluded. Other provider characteristics: NR
Bush, 1979 (Please refer to Boonacker, 2010 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Blaschke, 2014 United States Patient N = 1,166 sampled visits, extrapolated to 4.9 million estimated ED visits Provider N = NR Practice N = NR	Time of year/patterns of disease activity: flu seasons defined as October through April (inclusive), with patient visits from May through September excluded. Local tailoring: NR System-level characteristics: National Hospital Ambulatory Medical Care Survey (NHAMCS) samples visits to hospital EDs throughout the US, excluding Federal hospitals.	Reduced antibiotic prescribing for influenza (viral etiology, versus other respiratory illnesses like bacterial pneumonia), especially when diagnosis supported by RIDT.	NHAMCS uses "4-stage probability based sampling process" with sampling units based on geographic region, hospital, ED, and patient visits, and assigns weight accounting for sampling. Paper reports "differences in the percentage usage of each of the 3 clinical measures" across the 3 groups defined by RIDT use and flu diagnosis; it does not report any adjustment of these percent differences for factors likely affecting outcomes, though weights based on sampling design appear to be used in calculating CIs.
Bush, 1979 (Please refer to Boonacker, 2010 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Blaschke, 2014 United States Patient N = 1,166 sampled visits, extrapolated to 4.9 million estimated ED visits Provider N = NR Practice N = NR	Rate difference (95% CI) for weighted proportion of visits in which antibiotics were prescribed, compared with RIDT+/INF+: RIDT-/INF+: 12% (0% to 23%) RIDT+/INF-: 36% (25% to 46%) (RIDT + or - refers to whether test was conducted, not its result)	NR
Bush, 1979 (Please refer to Boonacker, 2010 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Blaschke, 2014 United States Patient N = 1,166 sampled visits, extrapolated to 4.9 million estimated ED visits Provider N = NR Practice N = NR	NR	Rate difference (95% CI) for weighted proportion of visits in which ancillary testing was performed (chest radiography, blood culture, urinalysis, and complete blood count), compared with RIDT+/INF+: RIDT-/INF+: 8% (-8% to 24%) RIDT+/INF-: 15% (0% to 30%) Rate difference (95% CI) for weighted proportion of visits in which antivirals were prescribed, compared with RIDT+/INF+: RIDT-/INF+: -37% (-52% to -22%) RIDT+/INF-: -54% (-68% to -40%) (RIDT + or - refers to whether test was conducted, not its result)
Bush, 1979 (Please refer to Boonacker, 2010 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Blaschke, 2014 United States Patient N = 1,166 sampled visits, extrapolated to 4.9 million estimated ED visits Provider N = NR Practice N = NR	NR	NR	
Bush, 1979 (Please refer to Boonacker, 2010 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Chowdhury, 2007 Bangladesh Patient N = NR for study population Provider N = NR Practice N = 24	Pre/post Retrospective baseline survey, with followup 3-4 months after intervention (dates NR).	Acute respiratory infections, no further criteria specified but WHO guidelines discussed which differentiate "pneumonia from cough and cold and malaria." Antibiotic prescribing outcome reported for "under five children" only.	"THCs doctors who were involved in prescribing at the outpatient departments."	Types: Multifaceted (Educational/Behavioral, Clinical and System-level) Target: providers Group I (STG + audit): WHO standard treatment guidelines (STG), describing signs and symptoms of pneumonia and how to differentiate from other diagnoses, "explained to the doctors in the THCs once" by a visiting pediatrician/clinician; auditing performed by providers and their colleagues, using WHO form to score prescriptions vs. STG (i.e. whether antibiotic prescribed in nonpneumonia patient.) Group II: STG only Group III: control
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Chowdhury, 2007 Bangladesh Patient N = NR for study population Provider N = NR Practice N = 24	Control THCs received no intervention.	NR	Age: antibiotic prescribing reported for under five children only (mean age NR) Other characteristics: NR	Specialty and years in practice: NR Type of clinic: outpatient departments of THCs Geographic region: Dhaka division, a large, central division, one of seven in Bangladesh.
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Chowdhury, 2007 Bangladesh Patient N = NR for study population Provider N = NR Practice N = 24	Time of year: NR Patterns of disease activity: NR Locally tailored: NR System-level characteristics: "government Thana health complexes (THCs), the primary health care centres of Bangladesh." A Thana is a subdistrict of one of the seven administrative divisions of Bangladesh.	Followed WHO guidelines (WHO/ARI/94, 31 January) for treatment of pneumonia vs. cough, cold, and other infections, where appropriateness defined by "whether antibiotic prescribed in non pneumonia patient." Unclear whether ARI definition includes pneumonia, and whether antibiotic prescribing outcome represents all antibiotic prescriptions or only inappropriate prescriptions.	Baseline antibiotic use only: study restricted to clinics with high (≥72%) baseline use, with further matching of intervention and control groups by baseline use, though methods for matching clinics and allocating to study group not described.
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Chowdhury, 2007 Bangladesh Patient N = NR for study population Provider N = NR Practice N = 24	"Antibiotic prescribing for ARI in under five children:" (post- vs. pre-intervention): STG + Audit: 67% vs. 90%, p<0.05 for 6/8 sites, p=NR overall STG only: 71% vs. 86%, p<0.05 for 3/8 sites, p=NR overall Control: 81% vs. 89%, p<0.05 for 4/8 sites, p=NR overall	NR
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Chowdhury, 2007 Bangladesh Patient N = NR for study population Provider N = NR Practice N = 24	NR	NR
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Chowdhury, 2007 Bangladesh Patient N = NR for study population Provider N = NR Practice N = 24	NR	NR	
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Gonzales, 1999 United States Patient N = 4,489 (2,462 at baseline, 2,027 in study period) Provider N = 93 Practice N = 4	Prospective nonrandomized controlled trial November 1996 - February 1997 (baseline) and November 1997 - February 1998 (study period).	Adults 18 years of age and older with an office visit for acute bronchitis, sinusitis, or URI during the baseline and study periods.	All clinicians caring for patients diagnosed as having the aforementioned conditions. Clinicians included board-certified internal medicine and family practice physicians, nurse practitioners, physician assistants, and registered nurses.	Type: Multifaceted Target: Providers and Patients Description: The full intervention site received household and office-based patient educational materials, as well as a clinician intervention consisting of education, practice-profiling, and academic detailing. Household educational materials included refrigerator magnets, CDC pamphlet "Your Child and Antibiotics - Sometimes Antibiotics Can Be Harmful", "Operation Clean Hands" pamphlet by Bayer Pharmaceutical Division, and letter describing study. Office-based educational materials included posters and information sheets. A limited intervention site received only office-based educational materials, and control sites provided usual care.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Gonzales, 1999 United States Patient N = 4,489 (2,462 at baseline, 2,027 in study period) Provider N = 93 Practice N = 4	Full intervention vs. Limited intervention vs. Control	Type of RTI: Uncomplicated acute bronchitis, sinusitis or URI Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Age Range: 49% 18 - 44 y % female: 54.3 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR	Specialty: Family medicine and internal medicine Number of years in practice: NR Type of Clinic: Primary care Geographical region: Denver-Boulder, Colorado Population served: 350,000

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Gonzales, 1999 United States Patient N = 4,489 (2,462 at baseline, 2,027 in study period) Provider N = 93 Practice N = 4	Time of year: November 1996 - February 1997 and November 1997 - February 1998 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Practices belonged to Kaiser Permanente, a nonprofit, group-model health maintenance organization	NR	Mixed-effects model, using PROC MIXED macro in SAS statistical application program, to control for potential clustering (random effects) of clinicians by site. Within-site analyses included month, patient age and sex, and clinician type and specialty as fixed effects. Between site analyses also included site as a fixed effect.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Gonzales, 1999 United States Patient N = 4,489 (2,462 at baseline, 2,027 in study period) Provider N = 93 Practice N = 4	Antibiotic Prescribing Rates Uncomplicated Acute Bronchitis Control vs. Limited Intervention vs. Full Intervention Study Period (rate[1], p for change) Full intervention: 74 vs. 48, 0.003 Limited intervention: 82 vs. 77, 0.68 Control: 78 vs. 76, 0.81 Between-site analysis confirms rate of change in monthly antibiotic prescription rates for uncomplicated acute bronchitis was greater at intervention site than at control and limited intervention sites (p=0.02) Uncomplicated URIs Antibiotic prescribing for uncomplicated URIs declined at all sites, between baseline and study periods, but to a similar extent at all sites (p>0.05 for all comparisons) Uncomplicated sinusitis Baseline vs. Study Period (rate[1]) Control: 88 vs. 88 Limited Intervention: 85 vs. 91 Full Intervention: 87 vs. 89	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects	KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics
Gonzales, 1999 United States Patient N = 4,489 (2,462 at baseline, 2,027 in study period) Provider N = 93 Practice N = 4	NR	Incident Office Visit Rates[2]* Control vs. Limited Intervention vs. Full Intervention Uncomplicated Acute Bronchitis Baseline Period: 17 vs. 28 vs. 18 Study Period: 15 vs. 18 vs. 15 Uncomplicated URIs Baseline Period: 50 vs. 46 vs. 60 Study Period: 49 vs. 40 vs. 58 Uncomplicated Sinusitis Baseline Period: 32 vs. 50 vs. 50 Study Period: 28 vs. 40 vs. 40 Nonantibiotic Medication Prescriptions for Patients with Acute Bronchitis (Absolute Change from Baseline to Study Period, %) Control vs. Limited Intervention vs. Full Intervention Bronchodilators: 11.0 vs. 9.8 vs. 15.3 Cough suppressants: 8.8 vs. 0.7 vs. 8.3 Analgesics: -0.2 vs. -1.6 vs. 0.2 Patients Returning for Care within 30 Days by Diagnosis (Absolute Change from Baseline to Study Period, %) Control vs. Limited Intervention vs. Full Intervention Acute bronchitis: -0.2 vs. 0.1 vs. -0.7 Pneumonia: 1.0 vs. 0.4 vs. -0.2 (p=0.08 compared with control)

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Gonzales, 1999 United States Patient N = 4,489 (2,462 at baseline, 2,027 in study period) Provider N = 93 Practice N = 4	NR	NR	[1]Antibiotic prescription rate was defined as the proportion (%) of incident office visits where the patient received an antibiotic prescription. [2]Incident office visit rate was per 1000 members per period and was defined as the first visit per patient per period for a given condition divided by the average total adult health plan membership during each period. *Data obtained from graphs only and are approximate values.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Gonzales, 2001 United States Patient N = 266 Provider N = NR Practice N = 2 (1 full-intervention clinic, 1 limited-intervention clinic [control])	Cross-sectional January 1 to April 30, 1999.	Consecutive adult patients in whom acute bronchitis was diagnosed at family practice or internal medicine departments.	Clinicians practicing in the Denver, Colorado metropolitan area in practices belonging to Kaiser Permanente of Colorado.	Type: Multifaceted Target: Patients and Providers Description: Full-intervention practice households were mailed educational packets (refrigerator magnets outlining prevention, self-care, when-to-seek-care strategies for ARI, CDC-developed educational brochures on careful antibiotic use, proper hand-washing techniques developed by Bayer Pharmaceuticals, Inc., and a letter from practice director announcing campaign). Office-level patient education included examination room posters and fact sheets on appropriate management of acute bronchitis. Clinician education consisted of 1-hour presentation covering management of acute bronchitis, current rates of antibiotic treatment of acute bronchitis, description of patient educational efforts, and practice tips on "how to say no" when patients request antibiotics. Limited-intervention group received only office-based educational materials.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Gonzales, 2001 United States Patient N = 266 Provider N = NR Practice N = 2 (1 full-intervention clinic, 1 limited-intervention clinic [control])	Full- vs. limited-intervention practices	Type of RTI: Acute bronchitis Types of Signs and Symptoms: NR Duration of Signs and Symptoms: < 4 days (33.7%), 4 to 7 days (34.6%), > 7 days (31.7%) When counting started for duration: NR	Age Range: Intervention clinic 41% 18 to 44 y, control clinic 37% 45 to 64 y % female: 59.6 Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: 57.0% Prior use of antibiotics: NR	Specialty: Mixed Number of years in practice: NR Type of clinic: Family practice or internal medicine departments Geographical region: Denver, Colorado metropolitan area Population served: NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness	Confounders and Method(s) Used to Control for Them
Gonzales, 2001 United States Patient N = 266 Provider N = NR Practice N = 2 (1 full-intervention clinic, 1 limited-intervention clinic [control])	Time of year: January 1 to April 30, 1999 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Medical office practices belonging to Kaiser Permanente of Colorado (a group-model managed care organization)	NR	Adjusted for patient-reported duration of illness before the office visit, previous illness experience, most important reason for visits (illness severity vs. to get an antibiotic vs. other), age, sex, and clinician specialty in multivariate logistic regression analyses.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Gonzales, 2001 United States Patient N = 266 Provider N = NR Practice N = 2 (1 full-intervention clinic, 1 limited-intervention clinic [control])	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Gonzales, 2001 United States Patient N = 266 Provider N = NR Practice N = 2 (1 full-intervention clinic, 1 limited-intervention clinic [control])	NR	Overall Patient Satisfaction with Visit* Control Clinic vs. Intervention Clinic (% of respondents) Poor: 3 vs. 3 Fair: 5 vs. 3 Good: 29 vs. 25 Very Good: 42 vs. 40 Excellent: 19 vs. 26 Participants Reporting High Satisfaction: "My overall satisfaction with my visit was 'very good' or 'excellent'" Control Clinic vs. Intervention Clinic: 63% vs. 69% Predictors of High Patient Satisfaction** with an Office Visit for Acute Bronchitis Treatment at intervention clinic: Adjusted[1] RR=1.1; 95% CI, 0.81 to 1.3

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Gonzales, 2001 United States Patient N = 266 Provider N = NR Practice N = 2 (1 full-intervention clinic, 1 limited-intervention clinic [control])	NR	NR	*Proportions were obtained from bar graphs only and are approximate values **Defined as patients reporting "very good" or "excellent" satisfaction [1]Adjusted for patient-reported duration of illness before the office visit, previous illness experience, reason for seeking care, age, sex, and clinician specialty

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Gonzales, 2004 United States Patient N = 4,270 patient visits (341 patient visits in intervention practices) Provider N = NR Practice N = 55 (4 intervention, 51 control)	Prospective, nonrandomized controlled trial Winter 2000/2001 and 2001/2002.	Consecutive patients enrolled in a Medicare managed care program that were diagnosed with ARIs.	Primary care providers working in ambulatory office practices in Denver metropolitan area.	Type: Multifaceted Target: Patients and Physicians Description: Appropriate antibiotic use and antibiotic resistance educational materials were mailed to intervention practice households. Waiting and examination room posters were provided to intervention office practices. Patient educational intervention was added to an ongoing physician-centered quality improvement project -- the Colorado Medical Society Joint Data Project on Careful Antibiotic Use.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Gonzales, 2004 United States Patient N = 4,270 patient visits (341 patient visits in intervention practices) Provider N = NR Practice N = 55 (4 intervention, 51 control)	Control practices	Type: Bronchitis, sinusitis, upper respiratory tract infection, pneumonia, pharyngitis Types of Signs and Symptoms: NR Duration of Signs and Symptoms: NR When counting started for duration: NR	Age Range: 56% aged 65 - 74 y % female: 62 Ethnicity: NR SES: NR Frailty: NR Comorbidities: 4.1% had chronic lung disease Prior RTIs: NR Prior use of antibiotics: NR	Specialty: Primary care Years in practice: NR Clinic: Ambulatory office practices Geographical region: Denver metropolitan area Population served: Participants of a Medicare managed care program

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Gonzales, 2004 United States Patient N = 4,270 patient visits (341 patient visits in intervention practices) Provider N = NR Practice N = 55 (4 intervention, 51 control)	Time of year: November 2001 to February 2002 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Medicare managed care program	NR	Chi-square and multivariate logistic regression analyses were performed to examine unadjusted and adjusted associations between patient characteristics and antibiotic prescription rates. Clustering adjustment was only performed at the practice level. Controlled for secular changes measured among control practices.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Gonzales, 2004 United States Patient N = 4,270 patient visits (341 patient visits in intervention practices) Provider N = NR Practice N = 55 (4 intervention, 51 control)	Antibiotic Prescription Rates (%) Before and After Intervention Control Practices: Baseline Period vs. Study Period Bronchitis: 59 vs. 56 Pharyngitis: 51 vs. 39 Pneumonia: 35 vs. 37 Sinusitis: 69 vs. 67 Upper respiratory tract infection: 26 vs. 27 Intervention Practices: Baseline Period vs. Study Period Bronchitis: 52 vs. 44 Pharyngitis: NR* vs. NR* Pneumonia: NR* vs. 30 Sinusitis: 76 vs. 67 Upper respiratory tract infection: 26 vs. 27	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Gonzales, 2004 United States Patient N = 4,270 patient visits (341 patient visits in intervention practices) Provider N = NR Practice N = 55 (4 intervention, 51 control)	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Gonzales, 2004 United States Patient N = 4,270 patient visits (341 patient visits in intervention practices) Provider N = NR Practice N = 55 (4 intervention, 51 control)	NR	NR	*NR due to fewer than 20 visits

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Gonzales, 2005 United States Patient N[ǂ] = 16,686 patient visits at baseline, 14,648 patient visits during study period Provider N[ǂ] = 1,629 at baseline, 1,193 during study period Practice N[ǂ] = 709 at baseline, 592 during study period	Nonrandomized controlled trial November 1, 2000 to February 28, 2001.	Children with pharyngitis and adults with acute bronchitis.	Primary care physicians including those providing care to children.	Type: Multifaceted Target: Patients and Providers Description: Campaign packets were mailed to households identified by participating practices. Household packets included bilingual introductory letter for Colorado Department of Public Health and Environment explaining Be S.M.A.R.T. campaign, CDC brochures on antibiotic resistance, refrigerator magnet, and reference card providing easy-to-read facts about symptoms and treatments for ARIs. Office-based materials, produced in English and Spanish, consisted of waiting room materials (CDC posters and patient reference cards) and examination room posters (containing "talking points" for providers to use in discussing appropriate antibiotic use for pharyngitis in children and bronchitis in adults). Intervention practices (prespecified geographical area in Denver metropolitan area) were compared with local and distant control practices.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Gonzales, 2005 United States Patient N[ǂ] = 16,686 patient visits at baseline, 14,648 patient visits during study period Provider N[ǂ] = 1,629 at baseline, 1,193 during study period Practice N[ǂ] = 709 at baseline, 592 during study period	Local and distant control practices (outside prespecified geographical area in Denver metropolitan area)	Type of RTI: Pharyngitis (in children) and acute bronchitis (in adults) Signs and Symptoms: NR Duration: NR	Age Range: 51-55% (baseline) and 50-51% (study period) aged 6-12 y in pediatric population, 57-60% (baseline) and 51-56% (study period) aged 18-44 y in adult population % female: 51-54% (baseline) and 53-55% (study period) in pediatric population, 54-62% (baseline) and 60-62% (study period) in adult population Ethnicity: NR SES: NR Frailty: NR Comorbidities: 0 - 1% chronic lung disease in adult population Prior RTIs: NR Prior use of antibiotics: NR	Specialty: Family practice, pediatrics, other Years in practice: NR Clinic: Private office practices Geographical region: Colorado Population served: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Gonzales, 2005 United States Patient N[ǂ] = 16,686 patient visits at baseline, 14,648 patient visits during study period Provider N[ǂ] = 1,629 at baseline, 1,193 during study period Practice N[ǂ] = 709 at baseline, 592 during study period	Time of year: Winter 2000-2002 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Managed care organizations	NR	Adjusted for time period, practice site, patient age, and physician specialty. Also included variable indicating whether the physician had received an individual antibiotic prescribing profile as part of Colorado's ongoing quality improvement program. Controlled for secular changes measured among control practices.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Gonzales, 2005 United States Patient N[ǂ] = 16,686 patient visits at baseline, 14,648 patient visits during study period Provider N[ǂ] = 1,629 at baseline, 1,193 during study period Practice N[ǂ] = 709 at baseline, 592 during study period	Adjusted* Antibiotic Prescription Rates for Children with Acute Pharyngitis Compared between Sites** (Baseline vs. Intervention Period Antibiotic Prescription Rates) Distant Control: 40 vs. 41 Local Control: 41 vs. 39 Intervention: 38 vs. 30 p (intervention vs. distant control)=0.18 p (intervention vs. local control)=0.48 p (local control vs. distant control)=0.18 Adjusted* Antibiotic Prescription Rates for Adults with Acute Bronchitis Compared between Sites** (Baseline vs. Intervention Period Antibiotic Prescription Rates) Distant Control: 51 vs. 45 Local Control: 55 vs. 49 Intervention: 60 vs. 35 p (intervention vs. distant control)=0.002 p (intervention vs. local control)=0.006 p (local control vs. distant control)=0.22	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Gonzales, 2005 United States Patient N[†] = 16,686 patient visits at baseline, 14,648 patient visits during study period Provider N[†] = 1,629 at baseline, 1,193 during study period Practice N[†] = 709 at baseline, 592 during study period	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Gonzales, 2005 United States Patient N[†] = 16,686 patient visits at baseline, 14,648 patient visits during study period Provider N[†] = 1,629 at baseline, 1,193 during study period Practice N[†] = 709 at baseline, 592 during study period	NR	NR	[†]Pediatric and adult population N's combined (separated by baseline and study period) *Adjusted for patient age, gender, physician specialty, and clustering by office practice, physician, and managed care organization **Antibiotic prescription rates are from bar graphs only and are approximately values

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Gonzales, 2008 United States Patient N = 2,158,288 (in 2002) and 2,176,687 (in 2003) estimated population of campaign community; 528,383 (in 2002) and 535,117 (in 2003) estimated population of comparison community Provider N = 1,167 Practice N = NR	Nonrandomized controlled trial November 2002 to February 2003.	General public and managed care enrollees residing in the mass media (2.2 million people) and comparison (0.53 million people) communities.	Physicians residing in the mass media (2.2 million people) and comparison (0.53 million people) communities.	Type: Educational Target: Mothers of patients (young children) and providers (primary care physicians) Description: Mass media campaign included purchased advertising (billboards, bus tails, bus stop posters, interior bus signs, and national Public Radio spots) and earned media. Spanish language public service announcement aired on local Spanish network. Physician advocacy activities enhanced advertising campaign by getting logos, messages, and materials into providers' offices. Office materials mailed to requesting physicians included waiting and examination room posters on appropriate antibiotic use for pharyngitis and bronchitis, patient brochures relating to appropriate antibiotic use and antibiotic resistance, and stethoscope clips with Get Smart logo.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Gonzales, 2008 United States Patient N = 2,158,288 (in 2002) and 2,176,687 (in 2003) estimated population of campaign community; 528,383 (in 2002) and 535,117 (in 2003) estimated population of comparison community Provider N = 1,167 Practice N = NR	Colorado Springs (comparison) community	NR	NR	Specialty: Mix (primary care physicians were targeted) Years in practice: NR Clinic: Ambulatory physician offices Geographical region: Colorado Population served: 2.2 million people in mass media communities and 0.53 million people in comparison communities

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Gonzales, 2008 United States Patient N = 2,158,288 (in 2002) and 2,176,687 (in 2003) estimated population of campaign community; 528,383 (in 2002) and 535,117 (in 2003) estimated population of comparison community Provider N = 1,167 Practice N = NR	Time of year: Winter 2002 to 2003 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Managed care organization	NR	Multivariable logistic regression analysis was used to analyze results from the telephone surveys adjusting for Spanish language, age, race, comorbidities, education, income, internet access at home, and children ≤ 5 at home.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Gonzales, 2008 United States Patient N = 2,158,288 (in 2002) and 2,176,687 (in 2003) estimated population of campaign community; 528,383 (in 2002) and 535,117 (in 2003) estimated population of comparison community Provider N = 1,167 Practice N = NR	Antibiotic Prescriptions Dispensed by Retail Pharmacies Mass media vs. comparison community in 2002: 1.08 million vs. 0.28 million P for decline in antibiotic prescribing in general population vs. MCO population after mass media campaign: p=0.30 vs. p=0.03 Net Differences and Statistical Significance of Differences in Antibiotic Prescribing Rates Before vs. After Mass Media Campaign General population: no difference[1], 0.30 MCO population: net decline[2], 0.02 Pediatric MCO members: net decline[3], 0.01 Adult MCO members: no difference[4], 0.09	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects	KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics
Gonzales, 2008 United States Patient N = 2,158,288 (in 2002) and 2,176,687 (in 2003) estimated population of campaign community; 528,383 (in 2002) and 535,117 (in 2003) estimated population of comparison community Provider N = 1,167 Practice N = NR	Office and ED Visits for Potential Complications of Acute RTIs Among Pediatric MCO Members (Rate per 1000) Comparison Community: Baseline Period (November 2001 to October 2002) vs. Intervention Period (November 2002 to October 2003) Pneumonia: 16.2 vs. 17.2 Orbital abscess: 0.1 vs. 0.5 Meningitis: 0.2 vs. 0 Peritonsillar abscess: 0.1 vs. 0.1 Brain abscess: 0 vs. 0 Sepsis: 0 vs. 0 Retropharyngeal abscess: 0 vs. 0 Epiglottitis: 0 vs. 0 Mass Media Community: Baseline Period (November 2001 to October 2002) vs. Intervention Period (November 2002 to October 2003) Pneumonia: 17.3 vs. 16.2 Orbital abscess: 0.5 vs. 0.6 Meningitis: 0.1 vs. 0.3 Peritonsillar abscess: 0.3 vs. 0.2 Brain abscess: 0 vs. 0.2 Sepsis: < 0.1 vs. < 0.1 Retropharyngeal abscess: < 0.1 vs. < 0.1 Epiglottitis: < 0.1 vs. 0 Δ Mass Media - Δ Comparison (95% CI) Per 1000 Pneumonia: -2.1 (-6.1 to 1.9) Orbital abscess: -0.3 (-0.8 to 0.3) Meningitis: 0.4 (-0.2 to 0.6) Peritonsillar abscess: -0.1 (-0.5 to 0.2) Brain abscess: 0.2 (-0.2 to 0.4) Sepsis: 0 (-0.4 to 0.3) Retropharyngeal abscess: 0 (-0.3 to 0.3) Epiglottitis: < -0.1 (-0.3 to 0.3)	Net Differences and Statistical Significance of Differences in Monthly Pediatric Office Visit Rates between Mass Media and Comparison Communities Pediatric MCO Members: net decline[5], 0.01 Emergency Department Utilization Comparison Community: Baseline Period (November 2001 to October 2002) vs. Intervention Period (November 2002 to October 2003) ARI visits: 23.9 vs. 32.1 non ARI visits: 309 vs. 355 Mass Media Community: Baseline Period (November 2001 to October 2002) vs. Intervention Period (November 2002 to October 2003) ARI visits: 37.7 vs. 32.8 non ARI visits: 477 vs. 472 Δ Mass Media - Δ Comparison (95% CI) Per 1000 ARI visits: -13.1 (-18.4 to -7.9) -16% net decrease non ARI visits: -51.0 (-65.4 to 35.7) -15.9% net decrease

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Gonzales, 2008 United States Patient N = 2,158,288 (in 2002) and 2,176,687 (in 2003) estimated population of campaign community; 528,383 (in 2002) and 535,117 (in 2003) estimated population of comparison community Provider N = 1,167 Practice N = NR	NR	NR	[1]No difference, mass media community received fewer antibiotic prescriptions before and after the campaign compared with comparison community [2]Net decline, mass media community received fewer antibiotic prescriptions after the campaign compared with comparison community [3]Net decline, mass media community received fewer antibiotic prescriptions after the campaign compared with comparison community [4]No difference, mass media community received more antibiotic prescriptions before and after the campaign compared with comparison community [5]Net decline, mass media community received fewer office visits after the campaign compared with comparison community

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Harris, 2003 United States Patient N = 1,518 (554 at baseline and 964 in study period) Provider N = 42 (17 nurse practitioners and 25 physicians) Practice N = NR	Prospective nonrandomized controlled trial October 2000 to April 2001.	All English- or Spanish-speaking adults 18 y of age and older who presented to the Walk-in Clinic with symptoms of an ARI (cough, sore throat, nasal congestion, ear ache).	All physicians and nurse practitioners who cared for patients diagnosed with ARIs in the baseline and study periods were included in the analysis.	Type: Educational Target: Patients and Providers Description: Intervention was composed of three components: (1) provider educational session based on recommendations for appropriate antibiotic use published by the Center for Disease Control and Prevention, (2) examination room posters were directed a providers, (3) computer-based, audio-visual, bilingual (English and Spanish) ICE module that communicated a likely illness diagnosis, self-care strategies, and the role of antibiotics (or lack thereof) in the management of their illness. Study period patients who completed the ICE module were classified as being exposed to the full intervention. Study period patients who did not complete the ICE module were classified as being exposed to the limited intervention.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Harris, 2003 United States Patient N = 1,518 (554 at baseline and 964 in study period) Provider N = 42 (17 nurse practitioners and 25 physicians) Practice N = NR	Baseline vs. Limited Intervention vs. Full Intervention	Type of RTI: URI/viral illness (50.1%), pharyngitis (23.4%), sinusitis < 7 days of illness (4.4%), sinusitis ≥ 7 days of illness (8.4%), bronchitis/cough (13.6%) Types of Signs and Symptoms: Cough, sore throat, nasal congestion, ear ache Duration of Signs and Symptoms: < 7 days (58.8%) When counting started for duration: NR	Age: 18-30 y (43.1%) % female: 59.7 Ethnicity: White (37.4%), Hispanic (44.5%), African American (12.5%), Other (5.6%) SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR	Specialty: Internist (59.5%), nurse practitioner (40.5%) Number of years in practice: NR Type of clinic: Walk-in Clinic (WIC) at Denver Health Medical Center (DHMC) Geographical region: Denver, Colorado Population served: 50% Hispanic, 25% Caucasian, 15% African American, 1% Native American. 71 % of patient charges at DHMC are for Medicaid, medically indigent, or self-paying patients who lack health insurance. Approximately 21% of all visits to the WIC are by patients who are monolingual Spanish.

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness	Confounders and Method(s) Used to Control for Them
Harris, 2003 United States Patient N = 1,518 (554 at baseline and 964 in study period) Provider N = 42 (17 nurse practitioners and 25 physicians) Practice N = NR	Time of year: October 2000 to April 2001 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Walk-in Clinic at Denver Health Medical Center	Based on Centers for Disease Control and Prevention recommendations/guidelines	Multivariable analyses were adjusted for race/ethnicity, tobacco use, provider type, and specific ARI diagnosis

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Harris, 2003 United States Patient N = 1,518 (554 at baseline and 964 in study period) Provider N = 42 (17 nurse practitioners and 25 physicians) Practice N = NR	Proportion of patients receiving antibiotics (%, p for intervention groups vs. baseline, p for intervention vs. intervention) Baseline vs. Limited Intervention vs. Full Intervention Bronchitis: 58 vs. 30 vs. 24, p< 0.001, NS Nonspecific URI: 14 vs. 3 vs. 1, p< 0.001, NS Pharyngitis*: 76 vs. 71 vs. 78, p=NS, NS Sinusitis < 7 days*: 85 vs. 62 vs. 82, 0.06 (limited intervention vs. baseline), p=NS Sinusitis ≥ 7 days*: 89 vs. 89 s. 97, p=NS, NS All ARI*: 45 vs. 31 vs. 35, p< 0.001, < 0.001	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Harris, 2003 United States Patient N = 1,518 (554 at baseline and 964 in study period) Provider N = 42 (17 nurse practitioners and 25 physicians) Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Harris, 2003 United States Patient N = 1,518 (554 at baseline and 964 in study period) Provider N = 42 (17 nurse practitioners and 25 physicians) Practice N = NR	NR	NR	*Proportions were obtained from bar graph only and are approximate values

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Hemo, 2009 Israel Patient N = 186,380 (101,401 in baseline winter, 84,979 in study winter) Provider N = NR Practice N = NR	Prospective observational study November 2004 - February 2006.	Pediatric population (< 18 y) of an HMO (Maccabi Healthcare Services).	NR	Type: Educational Target: Parents of patients (children) Description: The HMO conducted a comprehensive mass media campaign to increase public awareness of the misuse of antibiotics among the general public, focusing mainly on the inappropriate use of antibiotics in the treatment of influenza and upper respiratory infection (URI). The campaign consisted of radio and television advertisements in conjunction with a concurrent 4-part television series. The advertisements projected the general message that antibiotics are not an appropriate treatment for colds and other viral URIs. The television series presented the serious implications of misusing antibiotics.
Herman, 2009 (Please refer to Andrews, 2012 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Hemo, 2009 Israel Patient N = 186,380 (101,401 in baseline winter, 84,979 in study winter) Provider N = NR Practice N = NR	Precampaign (baseline) vs. Postcampaign (study period)	Type of RTI: URI (57.1% baseline winter, 53.2% study winter), otitis media (6.7% baseline winter, 7.6% study winter), pharyngitis (36.1% baseline winter, 39.2% study winter) Signs and Symptoms: NR Duration: NR	NR	Specialty: NR Years in practice: NR Clinic: NR Geographical region: Israel Population served: 1.7 million (approximately 25% of the Israeli population)
Herman, 2009 (Please refer to Andrews, 2012 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Hemo, 2009 Israel Patient N = 186,380 (101,401 in baseline winter, 84,979 in study winter) Provider N = NR Practice N = NR	Time of year: Winter Patterns of disease activity: Peak antibiotic use during January and February of every year Locally tailored: Yes System-level characteristics: Maccabi Healthcare Services (Israel's second largest HMO)	Antibiotics are not appropriate treatment for colds and other viral URIs	Used a binary logistic regression models adjusted for demographic factors (age, sex, religion, and immigration status) to compare rates of antibiotic purchase in the preintervention and postintervention periods of the study winter with the parallel periods in the preceding winter.
Herman, 2009 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Hemo, 2009 Israel Patient N = 186,380 (101,401 in baseline winter, 84,979 in study winter) Provider N = NR Practice N = NR	Antibiotic Purchasing Rates, OR; 95% CI URI Precampaign vs. Baseline Winter: OR=0.962; 95% CI, 0.891 to 1.039 Postcampaign vs. Baseline Winter: OR=0.749; 95% CI, 0.694 to 0.808 Otitis Media Precampaign vs. Baseline Winter: OR=0.970; 95% CI, 0.874 to 1.076 Postcampaign vs. Baseline Winter: OR=0.652; 95% CI, 0.591 to 0.718 Pharyngitis Precampaign vs. Baseline Winter: OR=0.968; 95% CI, 0.929 to 1.009 Postcampaign vs. Baseline Winter: OR=0.931; 95% CI, 0.890 to 0.973	NR
Herman, 2009 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Hemo, 2009 Israel Patient N = 186,380 (101,401 in baseline winter, 84,979 in study winter) Provider N = NR Practice N = NR	NR	NR
Herman, 2009 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Hemo, 2009 Israel Patient N = 186,380 (101,401 in baseline winter, 84,979 in study winter) Provider N = NR Practice N = NR	Parental Awareness of Appropriate Antibiotic Use (reported as mean score* (SD), F, p) Exposed vs. Unexposed to Media Campaign: 6.65 (1.6) vs. 6.29 (1.6), 4.18, 0.04	NR	*Mean of composite score reflecting agreement with standards of appropriate antibiotic use (scale of 1-9 with 9 being high level of agreement)
Herman, 2009 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Holloway, 2009 Nepal Patient N = 2,883 (pre+post) Provider N = NR Practice N = NR	Pre/post Intervention in mid-2003; indicators measured November/December 2002 and December 2003/January 2004 (winters).	Children under five with ARI in previous 2 weeks. Questions to caregivers on symptoms validated in baseline study against health workers' diagnoses of mild ARI ("common cold, runny nose, cough and cold" with no or mild fever) and severe ARI ("pneumonia, bronchopneumonia, severe chest infection, severe bronchitis and bronchiolitis").	No criteria specified. Districts remote with limited access to health workers. Study recruited local female community health volunteers (FCHVs) as educators, and interventions targeted private drug retailers among others.	Type: Educational Targets: Patients/children, mothers/families, drug retailers, other community members Description: "Training the trainers:" ten study team staff trained 419 others (district health staff, teachers, community members, students); child to child education administered by teachers in schools; street theater performances by children to mothers/community followed by group discussions with mothers led by local FCHVs; posters communicating ARI messages.
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Holloway, 2009 Nepal Patient N = 2,883 (pre+post) Provider N = NR Practice N = NR	Control districts did not receive intervention	Type of RTI: Baseline 196 severe ARI, 1317 mild ARI (all 4 districts) Signs and symptoms: NR in study population Duration: NR	NR	Provider characteristics: drug retailers (selling drugs mostly without prescriptions) and traditional healers are the main providers in study area. Health posts staffed by paramedical personnel with ≤ 1 year's training; "a doctor should be present at a district hospital," but if not, paramedical personnel prescribe. Geographical region: four remote, mostly roadless hill districts of Eastern Nepal Population served: rural, agricultural, "most households have no electricity or ventilation and use kerosene lamps and pine wood for lighting."
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Holloway, 2009 Nepal Patient N = 2,883 (pre+post) Provider N = NR Practice N = NR	Time of year, patterns of disease activity: winter Locally tailored: local community leaders, drug retailers and others developed action plans; local FCHVs recruited as educators; local teachers helped conduct surveys; local terms used for ARI and treatment in surveys; locally available safe home remedies recommended for mild ARI. System-level characteristics: districts are remote with government health facilities several hours' walk away; each district has a hospital and 9-10 health posts, but less than a third of the population visits health facilities.	Antibiotics for severe ARI/pneumonia, not for mild ARI (see Patient Population Criteria)	Yes: analyses using stratification or logistic regression models included ARI severity, time (pre/post), and intervention status
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Holloway, 2009 Nepal Patient N = 2,883 (pre+post) Provider N = NR Practice N = NR	Intervention impact, percent of each treatment indicator, intervention - control: $(Post\text{-}Pre)_I$ - $(Post\text{-}Pre)_C$ Antibiotic Rx (any class): Severe ARI: +21.4% Mild ARI +1.1%	NR
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Holloway, 2009 Nepal Patient N = 2,883 (pre+post) Provider N = NR Practice N = NR	NR	Intervention impact: $(Post\text{-}Pre)_I$ - $(Post\text{-}Pre)_C$ Consultation at a health post: Severe ARI: +12.6% Mild ARI: -9.5%
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Holloway, 2009 Nepal Patient N = 2,883 (pre+post) Provider N = NR Practice N = NR	NR	NR	Excluded several outcomes specific to setting: antibiotics from drug retailers without a prescription, consultation with FCHVs, treatment with locally-available home remedies
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Little, 2014 United Kingdom Patient N = 12,829 Provider N = 616 Practice N = NR	Prospective cohort	Sore throat as main symptom or pharynx abnormal on exam; duration ≤ 14 days; age ≥ 16.	General practitioners who prescribed immediate antibiotics to ≤ 50% for tonsillitis.	Type: Clinical Target: Patient Description: Prescribing strategies (immediate, delayed, no prescription)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Little, 2014 United Kingdom Patient N = 12,829 Provider N = 616 Practice N = NR	Immediate, delayed, or no prescription	Mean severity of sore throat and difficulty in swallowing on a 4-point Likert scale=3 Previous duration in days=4.7 (when counting started NR) 60% fever in past 24 hours Mean temperature (°C): 36.8 35.2% pus on tonsils 12.6% severely inflamed tonsils	Mean Age: 33.6 % female: 68% Ethnicity: NR SES: NR Educational level: NR Frailty: NR Comorbidities: NR Prior RTIs: NR Prior use of antibiotics: NR	Specialty and years in practice: NR Type of clinic: General practice Geographic region: Dhaka division, a large, central division, one of seven in Bangladesh

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness	Confounders and Method(s) Used to Control for Them
Little, 2014 United Kingdom Patient N = 12,829 Provider N = 616 Practice N = NR	Time of year: 11/10/06-6/1/09 Patterns of disease activity: NR Locally tailored: NA System-level characteristics: General practitioners in England and Wales	NR	Compared 3 models: (1) Multivariate analysis controlling for clustering and all covariates: number of medical problems, previous duration of illness (<3 days), very inflamed tonsils, the absence of cough or coryza, age, cervical glands, severity of sore throat, pus, fever in the past 24 h, muscle aches, headache, sex, smoker, feeling generally unwell, diarrhea, and disturbed sleep; (2) multivariate analysis controlling for clustering and only significant variables: inflamed tonsils, fever in the past 24 h, generally unwell, and disturbed sleep; (3) Multivariate analysis by stratified propensity score.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Little, 2014 United Kingdom Patient N = 12,829 Provider N = 616 Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Little, 2014 United Kingdom Patient N = 12,829 Provider N = 616 Practice N = NR	Developed complications: No antibiotic=45% vs immediate=46% vs delayed=14% Risk ratios (95% CI) for models 1-3: Immediate vs no: (1) RR=0.64; 95% CI, 0.43 to 0.97; (2) RR=0.62; 95% CI, 0.43 to 0.91; (3) RR=0.66; 95% CI, 0.43 to 1.03 Delayed vs no: (1) RR=0.58; 95% CI, 0.33 to 1.00; (2) RR=0.58; 95% CI, 0.34 to 0.98; (3) RR=0.61; 95% CI, 0.34 to 1.10	Reconsultation with new or nonresolving symptoms in month after the index consultation for models 1-3 Immediate vs no: (1) RR=0.76; 95% CI, 0.66 to 0.87; (2) RR=0.83; 95% CI, 0.73 to 0.94; (3) RR=0.76; 95% CI, 0.67 to 0.86 Delayed vs no: (1) RR=0.58; 95% CI, 0.47 to 0.70; (2) RR=0.61; 95%, 0.50 to 0.74; (3) RR=0.57; 95%, 0.47 to 0.68

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Little, 2014 United Kingdom Patient N = 12,829 Provider N = 616 Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Litvin, 2013 United States Patient N = 38,592 encounters over 27 months Provider N = 39 Practice N = 9	Time series Phase 1: 1/1/2010 to 3/31/11, Phase 2: 7/1/2011 to 3/31/2012.	Patients presenting with ARI symptoms and given one of the following respiratory diagnoses: allergic rhinitis, asthma, bronchitis or bronchiolitis, COPD exacerbation, influenza, laryngitis or tracheitis, otitis media, pharyngitis or tonsillitis, pneumonia, sinusitis, and URI. ARI encounter defined as encounter at which CDSS used and at least one respiratory diagnosis made.	Physicians, nurse practitioners, and physicians' assistants working in primary care practices in the Practice Partner Research Network (PPRNet).	Type: Multifaceted (Educational, Clinical, System-level) Target: Providers were primary target, with some patient education materials also made available Description: CDSS was an EHR-integrated progress note template available at point of care. Reflected CDC "Get Smart" guidelines with recommendations based on patient symptoms/duration, age, and exam findings. ARI diagnostic criteria (e.g. Centor criteria for streptococcal pharyngitis) and treatment recommendations provided including antibiotics when appropriate. Links to patient education materials. Multi-method intervention to encourage CDSS adoption included introductory meetings, site visits for education and CDSS training, EHR-based audit and feedback, and study-practice liaison personnel. Delayed prescribing strategy presented. Second phase included final site visit or webinar with practice performance review and evidence reviews.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Litvin, 2013 United States Patient N = 38,592 encounters over 27 months Provider N = 39 Practice N = 9	None (longitudinal)	Type of RTI: all those listed in Patient Population Criteria. Most common for adults: URI (27% of all respiratory diagnoses), acute sinusitis (25%), acute bronchitis or bronchiolitis (15%) Most common for children: URI (40%), suppurative otitis media (19%), streptococcal pharyngitis (11%) Signs/symptoms and duration: NR for study population	Characteristics: NR Adults (≥18y): 64% of encounters Children: 36%	Specialty: Internal medicine and pediatrics: 1/9 (11%) of practices, 3/39 (7.7%) of providers, 14% of ARI encounters Remainder family practice Years in practice: NR Type of clinic: primary care Geographical region: one practice each in states of NC, KY, WA, AK, AZ, MS, UT, GA, IL Population: NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Litvin, 2013 United States Patient N = 38,592 encounters over 27 months Provider N = 39 Practice N = 9	Time of year: January to March and July through March Patterns of disease activity: CDSS use peaked in winter (highest in February of each year) Locally tailored: NR System-level characteristics: primary care practice research network	Following CDC guidelines, inappropriate use includes (1) use for "diagnoses for which antibiotics are rarely appropriate (URI, acute bronchitis or bronchiolitis, acute nonstrep pharyngitis, laryngitis or tracheitis, influenza, nonsuppurative otitis media, asthma or allergic rhinitis)," and (2) use of any or broad-spectrum antibiotics for acute adult sinusitis or bronchitis	Yes: General linear mixed models for longitudinal analyses included time and "random practice effects". Practice-level observations weighted by "practices' numbers of ARI encounters during the quarter."

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Litvin, 2013 United States Patient N = 38,592 encounters over 27 months Provider N = 39 Practice N = 9	Percent change; 95% CI over entire study period: Inappropriate antibiotic use: Adults: +1.6%; 95% CI, -5.4 to 8.5 Children: -1.9%; 95% CI, -9.0 to 5.3 Delayed prescription: Adults: -1.1%; 95% CI,-3.9 to 1.6 Children: -2.9%; 95% CI, -4.6 to -1.1 Acute sinusitis in adults: Any antibiotic: +0.52% (-4.3 to 5.3) Broad spectrum: -20% (-31 to -8.6) Acute bronchitis in adults: Any antibiotic: +9.2% (-2.2 to 21) Broad spectrum: -12% (-26 to 2.7)	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Litvin, 2013 United States Patient N = 38,592 encounters over 27 months Provider N = 39 Practice N = 9	NR	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Litvin, 2013 United States Patient N = 38,592 encounters over 27 months Provider N = 39 Practice N = 9	NR	NR	"For all of these measures, use of antibiotics was calculated as the percentage of encounters at which any antibiotic was prescribed out of all encounters. Use of broad spectrum antibiotic was calculated as the percentage of encounters at which a broad spectrum antibiotic was prescribed out of all encounters at which any antibiotic was prescribed. Use of delayed prescriptions was calculated as the percentage of encounters at which a delayed prescription was prescribed out of all encounters at which any antibiotic was prescribed."

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Llor, 2011 Spain Patient N = 6,849 Provider N = 339 Practice N = NR	Pre/post (FIG and PIG groups) with post-intervention control group Time frame: first registry January/February 2008, second January/February 2009, each 3 weeks/15 working days.	Patients with pharyngitis, no further diagnostic criteria given.	General practitioners (GPs) from 8 autonomous communities participated in full intervention. Another group of GP's from Catalonia, another autonomous community, assigned to partial intervention. Selection criteria NR.	Type: Multifaceted Target: Providers and patients Description: Full intervention group (FIG): prescriber feedback; training on antibiotic use; clinical guidelines on RTI management; patient handouts on antibiotic use; access to and training in Strep A and CRP POC tests. Partial intervention group (PIG): FIG interventions other than workshop on diagnosis and use of RADTs; no access to RADT tests.
Llor, 2012 Spain Patient N = 836 Provider N = 267 Practice N = NR	Pre/post (FIG and PIG groups) with post-intervention control group Time frame: first registry January/February 2008, second January/February 2009.	Rhinosinusitis, no further diagnostic criteria given.	Not reported in this publication, but same groups and numbers of providers recruited as in earlier Happy Audit publications (see above). Those who registered patients with sinusitis included here.	Type: Multifaceted Target: Providers and patients Description: Full intervention group (FIG): prescriber feedback; training on antibiotic use; clinical guidelines on RTI management; patient handouts on antibiotic use; access to and training in CRP POC test. Partial intervention group (PIG): FIG interventions other than workshop on diagnosis and use of RADTs; no access to CRP.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Llor, 2011 Spain Patient N = 6,849 Provider N = 339 Practice N = NR	"Another group of professionals (control group) from another two Autonomous Communities only did the registry in 2009 with no previous intervention."	NR (all with pharyngitis)	NR	Specialty: general practice Years in practice, population: NR Type of clinic: primary care Geographical region: Spain
Llor, 2012 Spain Patient N = 836 Provider N = 267 Practice N = NR	Not reported in this publication, but same groups and numbers of providers recruited as in earlier Happy Audit publications (see above). Those who registered patients with sinusitis included here.	Type of RTI: all with rhinosinusitis Signs and symptoms: Fever (33%), cough (76%), odynophagia (20%), purulent rhinorrhea (18%) Duration of signs and symptoms: 7.4 days average When counting started: before first consultation	Age: 40 years % female: 65 Other characteristics NR	Specialty: general practice Years in practice, population: NR Type of clinic: primary care Geographical region: Spain

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Llor, 2011 Spain Patient N = 6,849 Provider N = 339 Practice N = NR	Time of year: two consecutive winter seasons Other factors NR	Antibiotics for bacterial but not viral pharyngitis. Outcome reported: antibiotic prescription for an episode of pharyngitis.	Yes: multilevel logistic regression model adjusted for use of RADTs, age, gender, presenting signs, diagnosis, and patient demand for antibiotics.
Llor, 2012 Spain Patient N = 836 Provider N = 267 Practice N = NR	Time of year: two consecutive winter seasons Other factors NR	No antibiotics for viral rhinosinusitis, and less use for bacterial ("despite the fact that bacteria are present in 60% of acute rhinosinusitis, most cases resolve spontaneously") Outcome: antibiotic prescription for rhinosinusitis	Yes: multilevel logistic regression model adjusted for use/results of CRP, age, gender, presenting symptoms/ signs, diagnosis, radiography, and patient demand for antibiotics.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Llor, 2011 Spain Patient N = 6,849 Provider N = 339 Practice N = NR	Adjusted odds ratio; 95% CI for prescription of antibiotics in intervention versus control groups: PIG before intervention: OR=0.62; 95% CI, 0.28 to 1.4 PIG after: OR=0.53; 95% CI, 0.23 to 1.2 FIG before: OR=0.54; 95% CI, 0.27 to 1.1 FIG after: OR=0.23; 95% CI, 0.11 to 0.47	NR
Llor, 2012 Spain Patient N = 836 Provider N = 267 Practice N = NR	Adjusted odds ratio; 95% CI for prescription of antibiotics in intervention versus control groups: PIG before intervention: OR=0.91; 95% CI, 0.61 to 1.4 PIG after: OR=0.65; 95% CI, 0.21 to 1.1 FIG before: OR=1.0; 95% CI, 0.66 to 1.6 FIG after: OR=0.12; 95% CI, 0.01 to 0.32	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Llor, 2011 Spain Patient N = 6,849 Provider N = 339 Practice N = NR	NR	NR
Llor, 2012 Spain Patient N = 836 Provider N = 267 Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Llor, 2011 Spain Patient N = 6,849 Provider N = 339 Practice N = NR	NR	NR	Happy Audit study
Llor, 2012 Spain Patient N = 836 Provider N = 267 Practice N = NR	NR	NR	Happy Audit study

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Llor, 2012 Spain Patient N = 5,385 Provider N = 338 Practice N = NR	Pre/post (FIG and PIG groups) with post-intervention control group Time frame: first registry winter of 2008, second winter of 2009, each 3 weeks/15 working days.	LRTI patients, no further diagnostic criteria given.	General practitioners (GPs) from 8 autonomous communities participated in full intervention. Another group of GP's from Catalonia, another autonomous community, assigned to partial intervention. Selection criteria NR.	Type: Multifaceted Target: Providers and patients Description: Full intervention group (FIG): prescriber feedback; training on antibiotic use; clinical guidelines on RTI management; patient handouts on antibiotic use; access to and training in CRP POC test. Partial intervention group (PIG): FIG interventions other than workshop on diagnosis and use of CRP; no access to CRP.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Llor, 2012 Spain Patient N = 5,385 Provider N = 338 Practice N = NR	As above: providers from two other autonomous communities registering patients in 2009 with no previous intervention.	Type of RTI: acute bronchitis (67%), acute exacerbations of CB/COPD (24%), pneumonia (8.5%)	NR	Specialty: general practice Years in practice, population: NR Type of clinic: primary care Geographical region: Spain

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Llor, 2012 Spain Patient N = 5,385 Provider N = 338 Practice N = NR	Time of year: two consecutive winter seasons Other factors NR	Antibiotics for bacterial but not viral lower respiratory tract infections (LRTI). Outcome: antibiotic prescription for LRTI.	Yes: multilevel logistic regression model adjusted for use/results of CRP, age, gender, comorbidity, presenting signs, duration of symptoms, diagnosis, radiography, and patient demand for antibiotics.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Llor, 2012 Spain Patient N = 5,385 Provider N = 338 Practice N = NR	Adjusted odds ratio; 95% CI for prescription of antibiotics in intervention versus control groups: PIG before intervention: OR=0.57; 95% CI, 0.30 to 1.1 PIG after: OR=0.42; 95% CI, 0.22 to 0.82 FIG before: OR=0.81; 95% CI, 0.46 to 1.4 FIG after: OR=0.22; 95% CI, 0.12 to 0.38	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Llor, 2012 Spain Patient N = 5,385 Provider N = 338 Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Llor, 2012 Spain Patient N = 5,385 Provider N = 338 Practice N = NR	NR	NR	Happy Audit study

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Llor, 2014 Spain Patient N=27,833 RTIs Provider N=309; 281 analyzed Practice N=NR	Pre/post Time frame: patients registered during 3 weeks in the winter months of 2008 (pre-intervention) and in early 2009 (post-intervention)	All patients with RTI, no further diagnostic criteria given.	Family physicians/GPs from 8 autonomous communities participated in full intervention. Another group of GP's from Catalonia, another autonomous community, assigned to partial intervention. Selection criteria NR.	Type: Multifaceted Target: Providers and patients Description: Full intervention group (FIG): prescriber feedback; training on clinical guidelines for RTI management; patient brochures; access to and training in Strep A and CRP POC tests. Partial intervention group (PIG): FIG interventions other than workshop on diagnosis and use of RADTs; no access to RADT tests.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Llor, 2014 Spain Patient N=27,833 RTIs Provider N=309; 281 analyzed Practice N=NR	For both full and partial intervention groups, antibiotic prescribing after intervention was compared to prescribing before.	Type of RTI: common cold 40%, otitis media 2.3%, sinusitis 2.8%,pharyngitis 15%, tonsillitis 6.9%, acute bronchitis 12%, CB/COPD exacerbation 4.2%, pneumonia 1.5%, influenza 8.9%, other RTI 4.9%, not specified 1.6% Types of signs and symptoms: fever 32%, cough 75%, purulent ear discharge 1.9%, odynophagia 43%, tonsillar exudate 5.3%, tender cervical glands 5.9%, dyspnea 9.3%, increased expectoration 20%, purulent sputum 8.9% Duration: NR	NR	Specialty: family/general practice Years in practice, population: NR Type of clinic: primary care Geographical region: Spain

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Llor, 2014 Spain Patient N=27,833 RTIs Provider N=309; 281 analyzed Practice N=NR	Time of year: winter 2008, "early 2009" Other factors NR	Appropriate use not defined. Outcome: antibiotic use, reported by respiratory diagnosis.	Yes: logistic regression model adjusted for age, gender, signs and symptoms, referral, antibiotic demand, and "burden of GPs."

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Llor, 2014 Spain Patient N=27,833 RTIs Provider N=309; 281 analyzed Practice N=NR	Adjusted odds ratio (95% CI) for prescription of antibiotics after vs. before intervention: Partial intervention group: Overall: 0.99 (0.89-1.1) Common cold: **4.6 (2.4-8.9)** Otitis: 1.3 (0.39-4.3) Sinusitis: 0.43 (0.14-1.3) Pharyngitis: 1.0 (0.68-1.6) Tonsillitis: 1.0 (0.58-1.9) Acute bronchitis: **0.61 (0.42-0.88)** CB/COPD exacerbation: 1.2 (0.61-2.2) Pneumonia: 1.2 (0.25-5.7) Influenza: 2.0 (0.60-6.5) Other RTI: 0.76 (0.37-1.6) Full intervention group: Overall: **0.50 (0.44-0.57)** Common cold: **0.03 (0.01-0.06)** Otitis: 0.48 (0.12-2.0) Sinusitis: 0.57 (0.18-1.8) Pharyngitis: **0.15 (0.09-0.25)** Tonsillitis: **0.18 (0.09-0.37)** Acute bronchitis: **0.31 (0.20-0.47)** CB/COPD exacerbation: **0.42 (0.19-0.90)** Pneumonia: 0.31 (0.04-2.6) Influenza: **0.01 (0.00-0.07)** Other RTI: **0.39 (0.17-0.93)**	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Llor, 2014 Spain Patient N=27,833 RTIs Provider N=309; 281 analyzed Practice N=NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Llor, 2014 Spain Patient N=27,833 RTIs Provider N=309; 281 analyzed Practice N=NR	NR	NR	Happy Audit study

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Mainous, 2013 United States Patient N = 35,417 at baseline (calc)[a] Provider N = 280 (calc)[b] Practice N = 70 (9 intervention, 61 control)	Time series 3 months before to 15 months after intervention (October 2009 through March 2011).	Acute respiratory infections, including diagnoses for which antibiotics are inappropriate and those for which antibiotics are indicated (see appropriateness definition).	Physicians, nurse practitioners, and physicians' assistants working in primary care practices in the Practice Partner Research Network (PPRNet).	Type: Multifaceted (Educational, Clinical, System-level) Target: Providers Description: CDSS was an EHR-integrated progress note template available at point of care. (Provider could choose to use CDSS or bypass it). Reflected CDC "Get Smart" guidelines with recommendations based on patient symptoms/duration, age, and exam findings. ARI diagnostic criteria, scoring strategies (e.g. Centor criteria for streptococcal pharyngitis) and treatment recommendations provided including antibiotics when appropriate. Multi-method intervention to encourage CDSS adoption included EHR-based audit and feedback, site visits for academic detailing (education), performance review, and training, and liaison personnel communicating between study and practices.
Maor, 2011 (Please refer to Andrews, 2012 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Mainous, 2013 United States Patient N = 35,417 at baseline (calc)[a] Provider N = 280 (calc)[b] Practice N = 70 (9 intervention, 61 control)	Control practices were unaware of the intervention; they received no information on the intervention or the CDSS and no educational materials.	NR	NR	Practice characteristics: Specialty: 89% family medicine Years in practice: NR Type of clinic: primary care Geographical region: 30% South, 30% Northeast, 24% Midwest, 16% West (overall; varies for intervention vs. control) Population served: NR
Maor, 2011 (Please refer to Andrews, 2012 systematic review)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Mainous, 2013 United States Patient N = 35,417 at baseline (calc)[a] Provider N = 280 (calc)[b] Practice N = 70 (9 intervention, 61 control)	Time of year: 4th quarter 2009 through 1st quarter 2011 Patterns of disease activity: seasonal; months 9 through 11 September-November 2010) were "immediately before the second ARI season." Locally tailored: NR System-level characteristics: primary care practice research network	Following CDC guidelines, diagnoses for which antibiotics are inappropriate comprise nonspecific upper respiratory infections, acute bronchitis, acute nonstreptococcal pharyngitis, and otitis media with effusion. Diagnoses for which antibiotics are indicated comprise acute sinusitis, streptococcal pharyngitis, pneumonia, acute otitis media, and chronic obstructive pulmonary exacerbations (in adults only).	Control practices matched to intervention practices by number of providers and baseline ARIs. Practice-level outcome observations weighted for number of ARI episodes in the quarter observed. Linear mixed models for longitudinal analyses adjusted for time, practice specialty, number of providers, region, and baseline ARIs, with an interaction term for time and intervention/control status.
Maor, 2011 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Mainous, 2013 United States Patient N = 35,417 at baseline (calc)[a] Provider N = 280 (calc)[b] Practice N = 70 (9 intervention, 61 control)	Intervention vs. control practices (See Comments for definitions): Change in inappropriate prescribing: Adults: -0.6% vs. +4.2% (p=0.03) Children: +1.4% vs. +4.2% (p=0.34) Use of broad-spectrum antibiotics: Adults: -17% vs. +1.2% (p<0.0001) Children: -20% vs. +0.9% (p<0.0001)	NR
Maor, 2011 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Mainous, 2013 United States Patient N = 35,417 at baseline (calc)[a] Provider N = 280 (calc)[b] Practice N = 70 (9 intervention, 61 control)	NR	NR
Maor, 2011 (Please refer to Andrews, 2012 systematic review)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Mainous, 2013 United States Patient N = 35,417 at baseline (calc)[a] Provider N = 280 (calc)[b] Practice N = 70 (9 intervention, 61 control)	NR	NR	Inappropriate prescribing "calculated by dividing the number of ARI episodes with diagnoses in the 'inappropriate' category that included an antibiotic prescription by the total number of ARI episodes with diagnoses for which antibiotics are 'inappropriate'." Broad-spectrum antibiotic use "calculated by dividing the number of all ARI episodes (episodes considered either inappropriate or appropriate for antibiotics) with a broad-spectrum antibiotic prescription by the total number of ARI episodes with an antibiotic prescription." Adjusted weighted mean change across practices between 12/2009 and 3/2011 reported.
Maor, 2011 (Please refer to Andrews, 2012 systematic review)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
McKay, 2011 Canada Patient N = 43,559 Provider N = 7,808 Practice N = NR	Ecological study September 1, 2005 to August 30, 2009.	Children in daycare (2 to 5 y) and their parents, grade 2 students (7 y) and their parents, older adults in assisted-living facilities and the general public of British Columbia.	Physicians and pharmacists in British Columbia.	Type: Educational Target: General public and health care professionals Description: Public education component included annual media campaigns, print material distribution, and audience-specific education curricula. Print material included signs, posters, stickers, activity placemats and a parent's guide to managing common infections. Media campaigns were aired on television and radio, and advertising appeared on transit routes and vehicles. Health care professional education arm offered accredited courses to physicians and pharmacists, with a focus on antibiotic use, resistance and strategies to prescribe appropriately.

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Comparator	Patient Characteristics: Type of RTI Types of Signs and Symptoms Duration of Signs and Symptoms When Counting Started for Duration	Patient Characteristics: Mean Age Percent Female Ethnicity SES Educational Level Frailty Comorbidities Prior RTIs Prior use of Antibiotics	Provider Characteristics: Specialty Number of Years in Practice Type of Clinic Geographical Region Population Served
McKay, 2011 Canada Patient N = 43,559 Provider N = 7,808 Practice N = NR	Preparticipation vs. postparticipation	NR	NR	Specialty: Physicians and pharmacists Number of years in practice: NR Type of clinic: NR Geographical region: British Columbia, Canada Population served: General public

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
McKay, 2011 Canada Patient N = 43,559 Provider N = 7,808 Practice N = NR	Time of year: September 2005 to August 2009 Patterns of disease activity: NR Locally tailored: Yes, local adaptation of 'Do Bugs Need Drugs?' intervention originally implemented in Alberta, Canada System-level characteristics: NR	Outlined in the 'Bugs & Drugs' book, a 'Do Bugs Need Drugs?'-endorsed antimicrobial reference guide	Descriptive statistical results are presented

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
McKay, 2011 Canada Patient N = 43,559 Provider N = 7,808 Practice N = NR	Mean Proportion of Antibiotic Use by RTI Preparticipation vs. Postparticipation (%, p) Acute Bronchitis: 34.6 vs. 21.4, p=0.023 All Indications: 45.6 vs. 39.2, p=0.019	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
McKay, 2011 Canada Patient N = 43,559 Provider N = 7,808 Practice N = NR	NR	NR

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
McKay, 2011 Canada Patient N = 43,559 Provider N = 7,808 Practice N = NR	Mean percentage of correct responses to quizzes by physicians before and after participating in the 2008 'Do Bugs Need Drugs?' Mainpro-C course Preparticipation (%) vs. Postparticipation (%) by Quiz Topic Bronchitis: 70.35 vs. 81.43 Otitis Media: 66.84 vs. 85.15 Sinusitis: 67.46 vs. 70.85 Pharyngitis: 73.33 vs. 90.16 Assessment of General Knowledge about Antibiotics and Resistance Percent improvement in correct responses after course, p: 11.2, p=0.013 Proportion of pharmacists who felt comfortable contacting a prescriber to suggest a change to an antibiotic prescription* Preparticipation vs. Postparticipation, p: 25.8 vs. 53.2, p< 0.001	NR	*Indication of improved shared decisionmaking between pharmacists and physicians or dissemination of improved knowledge?

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
McNulty, 2010 United Kingdom Patient N = 3,718 (1,888 precampaign and 1,830 postcampaign) Provider N = NR Practice N = NR	Before and after study January 2008 - January 2009.	Adults (aged ≥ 15 y) in either England or Scotland.	NR	Type: Educational Target: Adult patients Description: The English public antibiotics media campaign featured three posters displayed in magazines and newspapers. The key message of the posters was: 'The best way to treat most colds, coughs, and sore throats is plenty of fluids and rest. For advice talk to your pharmacist or doctor.' Copies of an A5 patient advice leaflet were given to patients instead of an antibiotic prescription upon visiting participating general practice surgeries and independent pharmacies. Extra copies were offered free of charge via phone, fax, or from the order line web site. A copy of the letter was also sent electronically to acute hospital trusts and health promotion units.

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Comparator	Patient Characteristics: Type of RTI Types of Signs and Symptoms Duration of Signs and Symptoms When Counting Started for Duration	Patient Characteristics: Mean Age Percent Female Ethnicity SES Educational Level Frailty Comorbidities Prior RTIs Prior use of Antibiotics	Provider Characteristics: Specialty Number of Years in Practice Type of Clinic Geographical Region Population Served
McNulty, 2010 United Kingdom Patient N = 3,718 (1,888 precampaign and 1,830 postcampaign) Provider N = NR Practice N = NR	Scottish survey respondents (control)	NR	NR	Specialty: Mix (general practice and pharmacy) Years in practice: NR Clinic: General practice surgeries and independent pharmacies Geographical region: UK Population served: General public

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
McNulty, 2010 United Kingdom Patient N = 3,718 (1,888 precampaign and 1,830 postcampaign) Provider N = NR Practice N = NR	Time of year: January 2008 to January 2009 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: National Health Service (NHS)-endorsed campaign	NR	Sampling weights provided by Ipsos MORI and based on the National Readership Survey to correct for known selection biases. Weights were defined by sex, household tenure, and white ethnicity and, within sex, by age, social grade, region and working status.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
McNulty, 2010 United Kingdom Patient N = 3,718 (1,888 precampaign and 1,830 postcampaign) Provider N = NR Practice N = NR	Reported Antibiotic Use by Respondents and Behavior of GPs (% Respondents, p) England 2008 vs. 2009; Scotland 2008 vs. 2009; England vs. Scotland 2009 Prescribed an antibiotic: 34 vs. 35, p=0.7; 29 vs. 35, p=0.4; p=1.0 Kept any leftover antibiotic: 2.2 vs. 7.0, p< 0.001; 0 vs. 4, p=0.04; p=0.4 Taken antibiotics without being told to do so: 8.3 vs. 7.8, p=0.8; 3 vs. 3, p=0.8; p=0.04 Asked GP or nurse for antibiotics in the past year: 28 vs. 29, p=0.7; 26 vs. 34, p=0.2; p=0.3 If respondent asked, prescribed antibiotic after some discussion: 82 vs. 73, p=0.07; 93 vs. 80, p=0.11; p=0.5 If respondent asked, prescribed antibiotic without discussion: 14 vs. 21, p=0.09; 7 vs. 12, p=0.47; p=0.3 If respondent asked, GP/nurse refused to prescribe antibiotic: 4 vs. 5, p=0.3; 0 vs. 8, p=0.2; p=0.7 Offered an antibiotic prescription to be cashed in at the pharmacy only if you felt no better, or felt worse, after several days: 11 vs. 13, p=0.4; 6 vs. 5, p=0.8; p=0.02 Offered the opportunity to return to surgery to pick up an antibiotic prescription only if you felt no better, or felt worse, after several days: 6 vs. 7, p=0.3; 6 vs. 3, p=0.3; p=0.1 Offered any type of delayed antibiotic prescription: 16 vs. 19, p=0.3; 12 vs. 8, p=0.4; p=0.01	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
McNulty, 2010 United Kingdom Patient N = 3,718 (1,888 precampaign and 1,830 postcampaign) Provider N = NR Practice N = NR	NR	Reported Antibiotic Use by Respondents and Behavior of GPs (% Respondents, p) England 2008 vs. 2009; Scotland 2008 vs. 2009; England vs. Scotland 2009 Advised about other remedies for cough and cold symptoms instead of being given an antibiotic prescription: 7.4 vs. 12.7, < 0.001; 7 vs. 8, 0.7; 0.3

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
McNulty, 2010 United Kingdom Patient N = 3,718 (1,888 precampaign and 1,830 postcampaign) Provider N = NR Practice N = NR	Reported Knowledge and Attitudes of Respondents to Antibiotics and Their Use (correct response in parentheses) (% Respondents incorrect/don't know, p) England 2008 vs. 2009; Scotland 2008 vs. 2009; England vs. Scotland 2009 Antibiotics work on most coughs and colds (disagree): 40 vs. 37, 0.3; 40 vs. 44, 0.6; 0.3 Antibiotics can kill bacteria (agree): 28 vs. 28, 0.8; 39 vs. 21, 0.004; 0.1 Antibiotics can kill viruses (disagree): 53 vs. 52, 0.7; 54 vs. 47, 0.5; 0.4 A course of antibiotics should be stopped when a person feels better (disagree): 30 vs. 26, 0.2; 29 vs. 18, 0.2; 0.2 If taken too often antibiotics are less likely to work in the future (agree): 15 vs. 16, 0.8; 10 vs. 10, 1.0; 0.1 It is OK to keep leftover antibiotics and use them later without advice from a doctor, nurse or pharmacist (disagree): 16 vs. 14, 0.4; 9 vs. 4, 0.3; 0.01 Antibiotics can kill the bacteria that normally live on the skin and in the gut (agree): 42 vs. 41, 0.8; 53 vs. 46, 0.3; 0.3 Bacteria that normally live on the skin and in the gut are good for your health (agree): 35 vs. 36, 0.6; 39 vs. 31, 0.4; 0.5 Resistance to antibiotics is a problem in British hospitals (agree): 30 vs. 37, 0.03; 32 vs. 29, 0.6; 0.2 Antibiotic-resistant bacteria could infect me and my family (agree): 32 vs. 33, 0.6; 27 vs. 29, 0.8; 0.5	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Perz, 2002 United States Patient N = 464,200 person-years over 3-year study Provider N = NR overall; 250 "key providers" and 1,500 physicians overall in intervention county Practice N = NR	Time series, though antibiotic use reported pre-post only 12-month periods before (May 1996 through April 1997), during (1997/98) and after (1998/99) the intervention.	Children younger than 15 years who were residents of four Tennessee counties and enrolled in the TennCare expanded Medicaid program. Children "not designated as either white or black" (4%) were excluded, as was person-time as a hospital inpatient. Respiratory illnesses included: outpatient diagnoses of otitis media, common cold, sinusitis, pharyngitis, tonsillitis, laryngitis/tracheitis, bronchitis, pneumonia and influenza, and unspecified ARI.	"250 key health care providers (e.g., pediatricians and family physicians) who provided most routine health care services to Knox County children." Not clear how these were identified. Newsletter sent to all county physicians.	Type: Educational Target: Providers, parents of young children, and the general public Description: Lectures by CDC physician to key providers; presentations at hospital events and clinics; prescribing guidelines distributed to key providers; newsletter articles to all county physicians; pamphlets to parents of newborns and children in daycare and grades Kindergarten through 3rd grade, to hospitals, clinics, dental offices and pharmacies, and to families receiving flu vaccines; patient education materials to key providers; media coverage and public service announcements.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Perz, 2002 United States Patient N = 464,200 person-years over 3-year study Provider N = NR overall; 250 "key providers" and 1,500 physicians overall in intervention county Practice N = NR	"Tennessee's 3 other urbanized counties" acted as controls; geographically distant from intervention county, with no similar community-wide intervention.	NR	Mean age NR; 8-9% <1 y, 30% 1 to <5y, 61-62% 5 to <15y % female: NR ("study populations similar with regard to age and sex") Ethnicity: 27% black in intervention county, 54 to 90% in 3 control counties SES: NR, but Medicaid an inclusion criterion Other patient characteristics: NR	Provider characteristics: NR overall (specialty included family practice and pediatrics for "key providers" in Knox county) Geographical region: four urban Tennessee counties Population: children on Medicaid

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness	Confounders and Method(s) Used to Control for Them
Perz, 2002 United States Patient N = 464,200 person-years over 3-year study Provider N = NR overall; 250 "key providers" and 1,500 physicians overall in intervention county Practice N = NR	Time of year: May through April, three successive years Patterns of disease activity: NR Locally tailored: NR System-level characteristics: TennCare managed care system extended health insurance coverage to more people than were eligible for Medicaid and shifted care to physicians in private practice	Not defined in outcomes measured, as individual antibiotic prescriptions not linked to diagnosis/indication. Messages of educational campaigns were that antibiotics should be used for bacterial infections only, that colds and most coughs and sore throats are caused by viruses and should not be treated with antibiotics, and that when used antibiotics should be narrow spectrum.	Yes: regression models for prescription rates adjusted for county, age, race, study year; antibiotic resistance stratified by study year and antibiotic category.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Perz, 2002 United States Patient N = 464,200 person-years over 3-year study Provider N = NR overall; 250 "key providers" and 1,500 physicians overall in intervention county Practice N = NR	Intervention-attributable change in antibiotic prescription rates (excess % reduction in prescription rates in Knox vs. control counties, by age and race; 95% CI): <1y, White: +2%; 95% CI, -5 to 8 <1y, Black: -16%; 95% CI, -20 to -12 1 to <5y, White: -8%; 95% CI, -13 to -4 1 to <5y, Black: -18%; 95% CI, -23 to -14 5 to <15y, White: -3%; 95% CI, -9 to 3 5 to <15y, Black: -20%; 95% CI, -25 to -15 All: -11%; 95% CI, -14 to -8 Intervention-attributable declines seen for all antibiotic categories except cephalosporins in white children (+11%; 95% CI, 5 to 16%; declines greater in control counties); declines statistically significant for penicillins and cephalosporins in black children and TMP-SMX in all children Ratio of antibiotic prescriptions to respiratory illness visits: White: -8% (-16 to 0) Black: -13% (-19 to 8)	Antibiotic resistance (proportion resistant among cases of invasive *Streptococcus pneumoniae* identified by ongoing surveillance in Knox county): Year 1 (n=20): Penicillin: 60% Cefotaxime: 55% TMP-SMX: 60% Erythromycin: 55% Year 3 (n=34): Penicillin: 71% Cefotaxime: 59% TMP-SMX: 65% Erythromycin: 50%

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Perz, 2002 United States Patient N = 464,200 person-years over 3-year study Provider N = NR overall; 250 "key providers" and 1,500 physicians overall in intervention county Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Perz, 2002 United States Patient N = 464,200 person-years over 3-year study Provider N = NR overall; 250 "key providers" and 1,500 physicians overall in intervention county Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Rattinger, 2012 United States Patient N = 3,831 Provider N = NR for study population (intervention was "part of a larger quality improvement initiative...used by at least 1379 unique providers during the study period.") Practice N = NR	Pre/post January 2002 to December 2006; intervention began January 2003 and continued through end of study period.	"Outpatients visits flagged by an ARI case-finding algorithm...if providers either assigned an ARI-related diagnostic code or prescribed a cough suppressant, and if the clinical note documented at least two ARI symptoms, as assessed by automated text analysis."	NR	Type: System-level Target: Providers Description: Intervention site: Veterans Affairs (VA) Maryland Health Care System. Clinical decision support system (CDSS) targeting gatifloxacin (fluoroquinolone) and azithromycin at the time of electronic prescription, with "drug-specific guideline recommendations as clickable choices during order entry". Cite 2001 publication describing guidelines developed by CDC. CDSS included treatment paths for pneumonia, bronchitis, sinusitis and nonspecific URI with diagnostic criteria and symptoms/signs suggesting antibiotic use appropriate. Providers could override CDSS recommendations.
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)				
Reyes-Morales, 2009 Mexico Patient N = 1,495 over course of study Provider N = 106 Practice N = NR	Time series Outcomes measured at baseline and after each stage of intervention (dates NR).	"ARI was defined as the presence of at least three of the following symptoms: runny nose, cough, malaise, fever, and/or sore throat for less than 2 weeks."	8 IMSS family medicine clinics, with 106 family physicians who agreed to participate.	Type: Multifaceted (Educational, Clinical, System-level) Target: Providers Description: Guideline development with algorithms based on clinical data and prognostic factors; training of clinical tutors; three-part educational intervention with interactive workshop sessions to discuss guidelines, individual tutorial with clinical tutor advising physician during patient visit, and peer review discussion of physicians' clinical cases.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Rattinger, 2012 United States Patient N = 3,831 Provider N = NR for study population (intervention was "part of a larger quality improvement initiative...used by at least 1379 unique providers during the study period.") Practice N = NR	VA Salt Lake City Health Care System	Type of RTI (one or more diagnosis per patient): pneumonia 14%, bronchitis 77%, pharyngitis 41%, sinusitis 19%, nonspecific ARI 4% Signs and symptoms and duration: NR	Mean age: 57 years % female: 7.7 % nonwhite: 66 SES, education, frailty, comorbidities, prior RTIs, prior antibiotics: NR	NR
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)				
Reyes-Morales, 2009 Mexico Patient N = 1,495 over course of study Provider N = 106 Practice N = NR	4/8 clinics with 58/106 physicians	NR	NR	Specialty: Family medicine 51.6% in intervention group, 57.8% in control Years of practice (median): 20 intervention, 21 control Type of clinic: NR Geographical region: 2 clinics in Mexico City, 4 in 2 northern states, two in one southern state

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Rattinger, 2012 United States Patient N = 3,831 Provider N = NR for study population (intervention was "part of a larger quality improvement initiative...used by at least 1379 unique providers during the study period.") Practice N = NR	Time of year: January 2002 to December 2006 Patterns of disease activity, local tailoring: NR System-level characteristics: Veterans Affairs Health Care Systems	Visits "reviewed for congruence with the guidelines" developed by the CDC. Antibiotics always appropriate for pneumonia, never for acute bronchitis or nonspecific URI, and sometimes for pharyngitis sinusitis if specific criteria met.	"Multivariable logistic regression and difference-in-difference regression analyses…were developed to estimate the impact of the CDSS intervention on overall antibiotics prescribing congruence." Regression models adjusted for age, marital status, sex, and race/ethnicity.
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)			
Reyes-Morales, 2009 Mexico Patient N = 1,495 over course of study Provider N = 106 Practice N = NR	Time of year, patterns of disease activity, and local tailoring: NR System-level characteristics: the Mexican Institute of Social Security (IMSS) is the largest public health care system in Mexico providing care to 45% of Mexican population	Appropriate if physician applied clinical guideline; antibiotics for pneumonia and for pharyngitis, otitis media and sinusitis associated with specific clinical signs and symptoms. No antibiotics for bronchiolitis, laryngotracheitis, asthma with ARI, rhinopharyngitis, vesicular pharyngitis, laryngitis, bronchitis.	There were "equal numbers of intervention and comparison clinics in each location," and "for each intervention clinic, the control clinic was similar in number of physicians, infrastructure, and population for which the clinic provided care." Not clear if similarity resulted from matching. Models adjusted for "cluster sampling of physicians," but adjustment for other confounders not discussed.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Rattinger, 2012 United States Patient N = 3,831 Provider N = NR for study population (intervention was "part of a larger quality improvement initiative...used by at least 1379 unique providers during the study period.") Practice N = NR	Relative risk of a congruent prescription, intervention vs. control: RR=1.24; 95% CI, 1.11 to 1.39 Targeted antibiotics: RR=2.57; 95% CI, 1.87 to 3.54 Antibiotics not targeted: RR=1.18; 95% CI, 0.69 to 2.01 "Adjusted multivariable difference-in-difference models between the two study sites, post- vs. pre-intervention periods" "We defined an ARI visit as 'congruent' with the guidelines if an antibiotic was either prescribed or withheld in accordance with the criteria" provided by CDC guidelines.	NR
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)		
Reyes-Morales, 2009 Mexico Patient N = 1,495 over course of study Provider N = 106 Practice N = NR	Appropriate prescription of antibiotics (difference of mean proportions vs. baseline; 95% CI): Post-workshop: Intervention: 14; 95% CI, 2.6 to 26 Control: -1.2; 95% CI, -11 to 8.3 Post-tutorial: Intervention: 11; 95% CI, -0.7 to 23 Control: -4.4; 95% CI, -14 to 5.3 Post-peer review: Intervention: 23; 95% CI, 10 to 35* Control: 1.5; 95% CI, -8.6 to 12 *p<0.05, intervention vs. control	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Rattinger, 2012 United States Patient N = 3,831 Provider N = NR for study population (intervention was "part of a larger quality improvement initiative...used by at least 1379 unique providers during the study period.") Practice N = NR	NR	NR
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)		
Reyes-Morales, 2009 Mexico Patient N = 1,495 over course of study Provider N = 106 Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Rattinger, 2012 United States Patient N = 3,831 Provider N = NR for study population (intervention was "part of a larger quality improvement initiative...used by at least 1379 unique providers during the study period.") Practice N = NR	NR	NR	
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)			
Reyes-Morales, 2009 Mexico Patient N = 1,495 over course of study Provider N = 106 Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Rubin, 2005 United States Patient N = 309 for chart review in intervention community, 17,483 for Medicaid data (354 of these in intervention community) (all pre+post) Provider N = NR Practice N = NR	Pre/post Intervention period: January through June 2001. Data collected retrospectively for intervention period and for baseline period of January through June 2000.	"acute URTI (e.g., pharyngitis, rhinosinusitis, otitis media, bronchitis, and nonspecific URTI)." "All patients presenting to their primary care professional with URTI symptoms were included in the study."	The two family practice groups in the study community, though one health care professional declined to participate (not clear whether this provider represented one of the two practices).	Type: Multifaceted (Educational, Clinical) Target: Patients, public, providers Description: Patient education materials, media campaign, physician small group session, algorithms for diagnosis and management of acute URTIs. Providers asked to use algorithms with ≥200 consecutive URTI patients.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Rubin, 2005 United States Patient N = 309 for chart review in intervention community, 17,483 for Medicaid data (354 of these in intervention community) (all pre+post) Provider N = NR Practice N = NR	Medicaid data for Community A compared with "the rest of rural Utah." Chart review data pre/post comparison only.	Type of RTI: Bronchitis (14% in intervention community at baseline), streptococcal (3%) and nonstreptococcal (23%) pharyngitis, otitis media (33%), sinusitis (7%), nonspecific URTI (19%). Signs/symptoms and duration: NR	Baseline data for residents of Community A overall (not limited to URTI patients included in study): Median age: 27.7 years % female: 49 Other patient characteristics: NR	Provider characteristics: NR Type of clinic: family practice in Community A, NR for "rest of rural Utah" Medicaid comparison group Geographical region/population served: Community A is a rural Utah community of <10,000 residents

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Rubin, 2005 United States Patient N = 309 for chart review in intervention community, 17,483 for Medicaid data (354 of these in intervention community) (all pre+post) Provider N = NR Practice N = NR	Time of year: January through June of two consecutive years. Pattern of disease activity: NR Locally tailored: NR System-level characteristics: rural Utah community, health care provided by 2 family practice groups	Algorithms focus on selecting narrower-spectrum antibiotics (e.g. amoxicillin) for streptococcal pharyngitis, acute otitis media, rhinosinusitis present for ≥ 14 days in children and ≥ 7 days in adults, and acute exacerbation of chronic bronchitis. Antibiotics not indicated for nonspecific URTI, croup, or bronchitis.	Logistic regression models for patient-level data included time, diagnosis and antimicrobial class.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Rubin, 2005 United States Patient N = 309 for chart review in intervention community, 17,483 for Medicaid data (354 of these in intervention community) (all pre+post) Provider N = NR Practice N = NR	Medicaid data: Difference in proportion of URTI episodes treated with antibiotics (baseline - intervention, positive values indicate decreased use) for Community A (intervention) vs. the rest of rural Utah (comparison); p-value for Community A vs. control: All URTI episodes: 15.6% vs. 1.5%, p=0.006, p=0.004 controlling for diagnoses Acute bronchitis: 56.1% vs. 1.7%, p=0.024 Pharyngitis, nonspecific URTI, acute sinusitis, otitis media: p=NS [Note: difficult to interpret highly-significant difference for all URTIs vs. generally not statistically significant differences for individual diagnoses.] By antimicrobial class: Macrolides: 13.4% vs. 0.2%, p<0.001 Cephalosporins, penicillins, quinolones: p=NS Medical record data: Difference in proportion of URTI episodes treated with antibiotics for Community A (intervention) only, p-value for intervention period vs. baseline period: p<0.05 for 3/3 macrolides, 1/3 penicillins, 4/4 cephalosporins, 1/2 quinolones	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Rubin, 2005 United States Patient N = 309 for chart review in intervention community, 17,483 for Medicaid data (354 of these in intervention community) (all pre+post) Provider N = NR Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Rubin, 2005 United States Patient N = 309 for chart review in intervention community, 17,483 for Medicaid data (354 of these in intervention community) (all pre+post) Provider N = NR Practice N = NR	NR	NR	Paper also reports local community pharmacy data, but prescriptions not linked to diagnoses and these aggregate data not abstracted. Apparent typographic error in Figure 2: chart review data for "urinary tract infection," vs. URTI in text of results.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Siegel, 2006 United States Patient N = 194 Provider N = 47 Practice N = NR	Pre/post Retrospective survey on antibiotic prescribing before (1/1999 to 1/2000) and after (1/2002 to 1/2003) the AOM/SNAP study (1/2000 to 12/2000).	Children age 1 to 12 with AOM. Exclusion criteria: temperature >101.5F, AOM symptoms >48 hours, another AOM episode within 3 months, child "toxic appearing," tympanic membrane "not intact" or "signs of impending perforation," immunodeficiency, coexisting bacterial infection.	Pediatricians in the Cincinnati Pediatric Research Group, a PBRN.	Type: Clinical Target: Families of pediatric patients Description: Families given Safety-Net Antibiotic Prescription (SNAP), a prescription given with instructions not to fill it unless child did not improve after 48 hours.
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Siegel, 2006 United States Patient N = 194 Provider N = 47 Practice N = NR	PBRN pediatricians compared with "30 randomly selected community pediatricians."	Type of RTI: acute otitis media Signs/symptoms and duration: NR	Age: 18% 1 to 2 years old, 82% >2 to 12 Other characteristics: NR	Specialty: pediatrics Years in practice: NR but "not statistically significantly different between the 2 groups" Type of clinic: primary care (NR for control providers) Geographical region: Cincinnati, Ohio Population served: community of 1.8 million
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)				

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Siegel, 2006 United States Patient N = 194 Provider N = 47 Practice N = NR	Time of year: intervention and before and after data collection periods each a full calendar year (January through December or through the following January) Patterns of disease activity, local tailoring: NR System-level characteristics: Practice-Based Research Network in Cincinnati, vs. community pediatricians with setting not further characterized	"Several investigators have demonstrated that antibiotics have a very modest benefit in most children with AOM" (with journal articles cited). Exclusion criteria (see population criteria) to identify severe or chronic disease. Families instructed not to fill antibiotic prescription if child improved by 48 hours.	Some outcomes for the two provider groups were compared before and after the SNAP intervention (i.e. minimal adjustment for time as a confounder).
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Siegel, 2006 United States Patient N = 194 Provider N = 47 Practice N = NR	Antibiotics for AOM: "Before the study, the majority of both groups, 51%, were using antibiotics almost all the time for AOM compared to 20% after the study, p<.001" Reporting unclear for: 1) Frequency definition (76 to 95% and >95% are options on questionnaire), and 2) whether 20% applied to both groups after study Use of SNAP: "Only one community pediatrician used SNAP before the study, while 8 used it afterward, p<.05" Not reported for PBRN physicians.	NR
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Siegel, 2006 United States Patient N = 194 Provider N = 47 Practice N = NR	NR for provider comparison groups	NR
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)		

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Siegel, 2006 United States Patient N = 194 Provider N = 47 Practice N = NR	NR	NR	
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)			

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Smeets, 2009 The Netherlands Patient N = NR Provider N = 382 providers Practice N = 141 (25 groups) (see Welschen, 2004)	Before/after	Patients from general practices within a geographically defined area in the middle region of the Netherlands	General practitioners in the predefined area of the Netherlands	Type: Multifaceted -Educational Target: Providers Description: Educational material given to providers based on the Dutch National Guideline for RTIs and given at educational meetings that included 1) group education meeting with a consensus procedure on indication and type of Abs for RTIs with academic detailing at the start of the intervention. -Communication Target: Providers Description: Communication skills training to make better agreements with patients about prescriptions. - System Target: Providers Description: Audit and feedback given on prescriptions.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Smeets, 2009 The Netherlands Patient N = NR Provider N = 382 providers Practice N = 141 (25 groups) (see Welschen, 2004)	Intervention (N=194): educational outreach visit including feedback, communication skills training, audit and feedback vs Control: no intervention, practices from the same region	NR	NR	Specialty: General practice Number of years in practice: NR Type of clinic: NR Geographical region: Europe Population served: 23-20% urban

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Smeets, 2009 The Netherlands Patient N = NR Provider N = 382 providers Practice N = 141 (25 groups) (see Welschen, 2004)	Time of year: January to June 2007 Patterns of disease activity: NR Locally tailored: yes, base don the Dutch national guideline for RTIs System-level characteristics: National Health Service	Based on national guidelines for antibiotics for RTI	Sorted out based on previous research protocols (see refs 26, 27)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Smeets, 2009 The Netherlands Patient N = NR Provider N = 382 providers Practice N = 141 (25 groups) (see Welschen, 2004)	Number of prescriptions per 1000 patients in the intervention and control group: 2006:+12% (206) vs +15% (202), NS 2007: +13% (232) vs +12% (227); -1% difference, NS	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Smeets, 2009 The Netherlands Patient N = NR Provider N = 382 providers Practice N = 141 (25 groups) (see Welschen, 2004)	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Smeets, 2009 The Netherlands Patient N = NR Provider N = 382 providers Practice N = 141 (25 groups) (see Welschen, 2004)	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Strandberg, 2005 Sweden Patient N = 14,719 visits Provider N = 80 Practice N = NR	Time series Time frame: "before, during, and after the initial audit registration, before interventions and feedback of the audit data". Registration during 5 weeks in April and May 1995. Data extracted for five 5-week time periods: A (six months before registration), B (immediately before), C (registration), D (immediately after), and E (three months after).	Diagnoses: upper respiratory tract infection, otitis media, sinusitis, tonsillitis, acute bronchitis, chronic obstructive lung disease, or pneumonia.	All general practitioners (GPs) at 14 public health centres.	Intervention type: System-level Target: Providers (N=45) who agreed to participate in audit Description: Intervention studied was "the effect of the actual registration process" on providers who agreed to participate in an "audit on treatment of respiratory tract infections (RTIs)", measured before the audit intervention actually takes place. "The question is whether the attentiveness that a registration entails leads to changed attitudes."

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Strandberg, 2005 Sweden Patient N = 14,719 visits Provider N = 80 Practice N = NR	Providers (N=35) who did not agree to participate in audit.	NR	NR	Specialty: 77.5% general practice, 5% locums, 17.5% residents Years in practice: NR Type of clinic: primary health care Geographical region: Blekinge county, Southern Sweden Population: 151,000 county inhabitants

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	Background Contextual Factors: Time of Year Patterns of Disease Activity Locally Tailored System-Level Characteristics	Definition of Appropriateness	Confounders and Method(s) Used to Control for Them
Strandberg, 2005 Sweden Patient N = 14,719 visits Provider N = 80 Practice N = NR	Time of year, patterns of disease activity: registration in April/May, followup for 5 weeks immediately after and also 3 months after (~August). "We found it possible but less likely that the reduction [in antibiotic use] had anything to do with seasonal variations." Local tailoring: NR System-level characteristics: "14 health centres and about 80 publicly employed GPs. Within the county there were in addition 12 private GPs, but they were excluded."	"The aim was to reduce the prescription of antibiotics for RTI, and to change prescriptions towards a greater proportion of Penicillin V (PcV), with a reduction in the prescription of broad-spectrum drugs." No authority cited or definition of broad-spectrum antibiotic given.	Stratified time series analysis only: results reported for each of five time periods, but no adjustment for other confounders.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Strandberg, 2005 Sweden Patient N = 14,719 visits Provider N = 80 Practice N = NR	Percentage of visits for RTI resulting in antibiotic prescription in each time period, A-E, participants vs. nonparticipants: A: RR=0.92; 95% CI, 0.87 to 0.97 B: RR=0.87; 95% CI, 0.82 to 0.92 C: RR=0.96; 95% CI, 0.90 to 1.0 D: RR=0.96; 95% CI, 0.89 to 1.0 E: RR=0.88; 95% CI, 0.81 to 0.95 Percentage of prescriptions of Penicillin V and broad-spectrum antibiotics of all antibiotics prescriptions in each time period, participants vs. nonparticipants: A: PcV RR=1.2; 95% CI, 1.1 to 1.3 Broad: RR=0.90; 95% CI, 0.79 to 1.0 B: PcV RR=1.1; 95% CI, 1.0 to 1.2 Broad: RR=0.89; 95% CI, 0.78 to 1.0 C: PcV RR=1.1; 95% CI, 1.0 to 1.2 Broad: RR=0.99; 95% CI, 0.85 to1.2 D: PcV RR=1.0; 95% CI, 0.93 to 1.1 Broad: RR=1.1; 95% CI, 0.93 to 1.3 E: PcV RR=0.94; 95% CI, 0.85 to 1.0 Broad: RR=1.0; 95% CI, 0.83-1.2	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Strandberg, 2005 Sweden Patient N = 14,719 visits Provider N = 80 Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Strandberg, 2005 Sweden Patient N = 14,719 visits Provider N = 80 Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Trepka, 2001 United States Patient N = 365 Provider N = NR Practice N = NR	Pre/post Baseline survey June/July 1997, intervention September-December 1997, post-intervention survey June-August 1998.	Household caregivers of children < 4 years surveyed (nonparent caregivers excluded from analyses). Diagnoses included in survey question on antibiotic indications: bronchitis, colds, dry cough, flu, nonstreptococcal sore throat.	"Primary care clinicians" and "staff at each primary care clinic."	Type: Educational Target: Patients and their parents, providers Description: Intervention conducted in northern Wisconsin (MESA-North). Parent and patient education: CDC pamphlet distributed to clinics, pharmacies, child care facilities; CDC posters to clinics and community organizations; presentations by nurse educators to parents and staff at child care centers, public health departments, schools, community organizations; newspaper articles on antibiotic resistance. Physician education: nurse educator presentations to primary care clinic staff; grand rounds presentation by study investigator; small-group teaching or telephone discussions with a physician educator; distribution of guidelines, fact sheets, and patient education materials.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Trepka, 2001 United States Patient N = 365 Provider N = NR Practice N = NR	Control area was the MESA-Central region, comprising 14 zip codes in central Wisconsin	NR	Patient characteristics (intervention + control): Age: NR % female: NR Race: 98% white, 2% nonwhite Ethnicity: 98% non Hispanic, 2% Hispanic SES, child's insurance: 75% private, 25% medical assistance Education (caregiver): 35% high school only, 65% some college	Provider characteristics: Specialty, type of clinic: primary care Years in practice: NR Geographical region: intervention conducted in 3 counties and 2 adjacent cities in northern Wisconsin; outcome survey conducted in the 8-zip code MESA-North region, a subarea of the intervention region. Population served: intervention population (MESA-North): population 27,692 (957 children <4); control 58,910 (2,655 <4)

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Trepka, 2001 United States Patient N = 365 Provider N = NR Practice N = NR	Time of year: surveys 2 consecutive summers, intervention September to December Patterns of disease activity: NR Locally tailored: NR System-level characteristics: Study conducted in the Marshfield Epidemiologic Study Area (MESA), a defined geographic region with care provided by Marshfield Clinic regional network and subject sampling frame available for research. Intervention conducted by Marshfield Medical Research Foundation.	Survey question on whether antibiotics were indicated for 5 diagnoses (see Comments), where "higher scores indicated less accurate knowledge regarding indications for antibiotic use." Educational pamphlet "provides examples of when antibiotics are and are not needed for children (e.g., rarely for bronchitis, not for colds)."	Yes: cofactors associated with post-intervention knowledge outcomes in univariate analysis ($p<0.1$) were entered into multivariate models. For ARA these were intervention area residence, preintervention ARA, parent & child ages, and exposure to interventions. For antibiotic indications score, univariate analysis showed no significant associations and unadjusted scores were reported.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Trepka, 2001 United States Patient N = 365 Provider N = NR Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Trepka, 2001 United States Patient N = 365 Provider N = NR Practice N = NR	NR	Patient satisfaction: "Percentage of parents who brought their child to another physician because they did not receive an antibiotic decreased from 4.6% to 1.7% in the intervention area and increased in the control area from 2.2% to 3.8%. The difference between the 2 area changes was -4.5%; 95% CI, -8.0 to -0.9; p=0.02."

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Trepka, 2001 United States Patient N = 365 Provider N = NR Practice N = NR	(See Comments for outcome definitions) Factors associated with high post-intervention ARA in final multivariate model included exposure to 2 or more local interventions: OR=1.9; 95% CI, 1.1 to 3.1 Univariate comparison of high ARA, difference of proportions, $(Post\text{-}Pre)_I$ - $(Post\text{-}Pre)_C$: +10% (95% CI +1.9% to +18%) Mean antibiotic indications scores, intervention vs. control areas: Preintervention: 3.9 vs. 4.3, p=0.07 Postintervention: 2.7 vs. 3.5, p<0.001	NR	Outcome definitions: Antibiotic resistance awareness (ARA): high level of ARA defined as agreement with each of 3 statements on antibiotic overuse and resistance. Antibiotic indications score: using survey question on whether antibiotics are indicated for 5 respiratory diagnoses (bronchitis, cold, dry cough, flu, nonstreptococcal sore throat), "always", "sometimes," and "never" were assigned scores of 2, 1, and 0, respectively.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Vinnard, 2013 United States Patient N = 3,421 (total patient visits pre + post) Provider N = 98 Practice N = NR	Prospective cohort study, with providers followed over time with pre/post intervention assessments for Academic detailing (AD) study and four time points for PM study. AD study: patient visits assessed during 1998 (baseline) and 2000, with intervention conducted in 1999. PM study: intervention conducted 9/1/01 to 1/1/02, with patient visits assessed during 4 time periods: 1/1/01 to 8/31/01, 1/1/00 to 8/31/00, 1/1/02 to 8/31/01, and 1/1/03 to 8/31/03.	Upper respiratory infections: acute bronchitis, cough, acute pharyngitis, acute URI, all by ICD-9 codes.	Academic detailing study: Intensive intervention group: 7 faculty providers with highest baseline antibiotic use for acute bronchitis Mild intervention group: 7 faculty providers with next highest baseline antibiotic use Patient mailing study: Intervention group: faculty providers with highest number of visits for the inclusion diagnoses (N=48 in results).	Academic detailing study: Type: Multifaceted Target: Providers and patients Description: Intensive intervention: a pharmacist and the director of the hospital Antimicrobial Stewardship Program met with each provider, presented published literature, and gave "provider-specific evaluation results," along with patient education materials. Mild intervention: patient education materials alone mailed to providers. Patient mailing study: Type: Educational Target: Patients Description: Educational brochure and explanatory letter signed by provider or Antimicrobial Stewardship director mailed to providers' patients with previous URI diagnoses.
Weiss, 2011 Canada Patient N = Population of Quebec Provider N = Unclear Practice N = NR	Time-series April 2005 to December 2007	Patients filling prescriptions at pharmacies in Quebec that are part of the IMS Health database	"All physicians and pharmacists in Quebec."	Type: Educational Target: Clinicians Description: Eleven 2-page guidelines with information on prescribing antibiotics for lower and upper respiratory tract infections, urinary tract infections and C. difficile infections were distributed along with letters from key stakeholders. CME and medical schools were encouraged to promote the guidelines.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Vinnard, 2013 United States Patient N = 3,421 (total patient visits pre + post) Provider N = 98 Practice N = NR	Academic detailing study: no intervention group of 14 nonfaculty providers Patient mailing study: control group were nonfaculty providers with highest number of visits for inclusion diagnoses (N=22 in results)	NR	NR	Geographical region: Pennsylvania Other characteristics: NR
Weiss, 2011 Canada Patient N = Population of Quebec Provider N = Unclear Practice N = NR	Pre-period. Other interventions are noted to possibly have been going on at the same time.	NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Vinnard, 2013 United States Patient N = 3,421 (total patient visits pre + post) Provider N = 98 Practice N = NR	Time of year: NR for AD study, February through August for PM study Patterns of disease activity, local tailoring: NR System-level characteristics: Clinical Practices of the University of Pennsylvania (CPUP) practice providers are university faculty; Clinical Care Associates (CCA) providers are nonfaculty but affiliated with the university.	Study outcome is proportion of visits for acute bronchitis or URI for which antibiotics prescribed. Limited reporting of broad- versus narrow-spectrum antibiotic use for PM study.	Intervention and control providers matched for baseline bronchitis visits. Models of effects of intervention on antibiotic prescribing included provider, time, and a time/ intervention interaction term. AD model also adjusted for sex and smoking.
Weiss, 2011 Canada Patient N = Population of Quebec Provider N = Unclear Practice N = NR	NR	No clear definition provided.	Analysis of prescribing over time only.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Vinnard, 2013 United States Patient N = 3,421 (total patient visits pre + post) Provider N = 98 Practice N = NR	AD study: Adjusted odds ratio; 95% CI for reduction in antibiotic use over time in intervention vs. control groups: Intensive intervention (with academic detailing): OR=2.8; 95% CI, 1.3 to 6.0 Mild intervention (patient materials only): OR=1.7; 95% CI, 0.7 to 3.8 PM study: Change in prescribing rate, pre/post time points pooled: Intervention group: 19% vs. 14% (-4.7%) Control group: 58% vs. 59% (+1.2%) p=0.13, intervention vs. control	NR
Weiss, 2011 Canada Patient N = Population of Quebec Provider N = Unclear Practice N = NR	Total outpatient antibiotic prescriptions per 1000 population: 471 vs 526; 10.5% lower Decreased by 4.2% in the first year after implementation (2005; p=0.002)	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Vinnard, 2013 United States Patient N = 3,421 (total patient visits pre + post) Provider N = 98 Practice N = NR	NR	NR
Weiss, 2011 Canada Patient N = Population of Quebec Provider N = Unclear Practice N = NR	NR	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making**	**KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding**	**Comments**
Vinnard, 2013 United States Patient N = 3,421 (total patient visits pre + post) Provider N = 98 Practice N = NR	NR	NR	Two substudies included: academic detailing (AD) and patient mailing (PM)
Weiss, 2011 Canada Patient N = Population of Quebec Provider N = Unclear Practice N = NR	NR	NR	

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Study Design (e.g. pre/post, time series)** **Time frame**	**Patient Population Criteria**	**Provider Population Criteria**	**Intervention Strategy Type:** **(1) Educational/Behavioral** **(2) Communication** **(3) Clinical** **(4) System-level** **(5) Multifaceted** **Target of Intervention (patient, provider, etc.)** **Intervention Description**
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)				
Wutzke, 2007 Australia Patient N = 12,217 Provider N = 5,758 Practice N = NR	Before/after study 1999 baseline, 2000 - 2004 intervention years	Australian population aged 15 y and over (national annual surveys of consumers) or aged 18 y or over (national omnibus surveys of consumers)	General practitioners and pharmacists	Type: Educational Target: Consumers (general public) and health professionals (general practitioners and pharmacists) Description: Small scale media-based community awareness campaign conducted via radio, television, and newspaper coverage in 2000. Larger scale interventions for consumers were implemented during the winter months in 2001, 2002, 2003, and 2004. Large scale intervention included persuasive message/tag line, various printed and electronic resources (information brochure for adults; posters for general practice, pharmacies, schools, and community centers; stickers and badges; prescription pads for symptomatic management and patient information leaflets distributed to GPs), mass media strategies including billboards, television, radio, and magazines. Small grants provided to community groups to implement community-based education sessions in 2001, 2002, and 2004.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Comparator**	**Patient Characteristics:** **Type of RTI** **Types of Signs and Symptoms** **Duration of Signs and Symptoms** **When Counting Started for Duration**	**Patient Characteristics:** **Mean Age** **Percent Female** **Ethnicity** **SES** **Educational Level** **Frailty** **Comorbidities** **Prior RTIs** **Prior use of Antibiotics**	**Provider Characteristics:** **Specialty** **Number of Years in Practice** **Type of Clinic** **Geographical Region** **Population Served**
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)				
Wutzke, 2007 Australia Patient N = 12,217 Provider N = 5,758 Practice N = NR	Pre-campaign vs. Post-campaign	NR	NR	Specialty: General practice and pharmacy Number of years in practice: NR Type of clinic: General practices and pharmacies Geographical region: Australia Population served: General public

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**Background Contextual Factors:** **Time of Year** **Patterns of Disease Activity** **Locally Tailored** **System-Level Characteristics**	**Definition of Appropriateness**	**Confounders and Method(s) Used to Control for Them**
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)			
Wutzke, 2007 Australia Patient N = 12,217 Provider N = 5,758 Practice N = NR	Time of year: Winter months (June - August) in 2000, 2001, 2002, 2003, and 2004 Patterns of disease activity: NR Locally tailored: Yes System-level characteristics: Australia's National Prescribing Service undertook campaign	NR	National annual surveys of consumers were stratified by age, gender, and region. National omnibus surveys of consumers were stratified by postcode area, age, and gender. For all consumer surveys, frequency distributions of weighted data were calculated for all variables. Analysis of drug utilization by Medicare Australia database involved augmented regression, which included seasonality, autocorrected error terms, and one point in the regression model to indicate the timing of the first intervention in 1999.

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ1 outcomes: Appropriate prescription and use of antibiotics**	**KQ2 outcomes: Antibiotic resistance**
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)		
Wutzke, 2007 Australia Patient N = 12,217 Provider N = 5,758 Practice N = NR	Proportion of the community reporting taking antibiotics when ill with last cough, cold, or flu 1999 % vs. 2000 % (change, p) vs. 2001 % (change, p) vs. 2003 % (change, p) vs. 2004 % (change, p): 10.8 vs. 10.0 (- 0.8, NS) vs. 10.1 (- 0.7, NS) vs. 9.8 (- 1.0, NS) vs. 7.4 (- 3.4, p< 0.05; 95% CI, 1.3 to 5.5 Median number of original antibiotic prescriptions for nine antibiotics commonly used for URTI decreased at a rate of 0.18 prescriptions per 1000 consultations per GP per month ($p < 0.0001$), equating to a decrease of 10.8 original antibiotic prescriptions per GP per year or 216,000 fewer PBS subsidized antibiotic prescriptions per year (given the approximate 20,000 GPs in Australia provide an average of 6,000 consultations per year)	NR

Author, Year **Country** **Patient Sample Size** **Provider Sample Size** **Practice Sample Size**	**KQ3 outcomes: Mortality, hospital admission, medical complications, adverse drug effects**	**KQ4 outcomes: Clinic/ED visits, time to return to work/school, patient satisfaction, quality of life, symptom improvement, use of nonantibiotic treatments, utilization of vaccinations, quality metrics**
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)		
Wutzke, 2007 Australia Patient N = 12,217 Provider N = 5,758 Practice N = NR	NR	Proportion of the community reporting actions when ill with last cough, cold, or flu 1999 % vs. 2000 % (change, p) vs. 2001 % (change, p) vs. 2002 % (change, p) vs. 2003 % (change, p) vs. 2004 % (change, p) Took nonprescription medicine: 67.5 vs. 68.9 (+ 1.4, NS) vs. 69.4 (+ 1.9, NS) vs. 70.5 (+ 3.0, NS) vs. 70.1 (+ 2.6, NS) Rested at home: 56.8 vs. 54.4 (-2.4, NS) vs. 53.7 (-3.1, NS) vs. 60.7 (+ 3.9, NS) vs. 57.5 (+ 0.7, NS) Asked pharmacists for advice: 20.2 vs. 20.6 (+ 0.4, NS) vs. 21.9 (+ 1.7, NS) vs. 22.4 (+ 2.0, NS) vs. 22.4 (+ 2.2, NS) Visited a doctor: 23.3 vs. 21.8 (- 1.5, NS) vs. 19.3 (- 4.0, NS) vs. 20.3 (- 3.0, NS) vs. 18.0 (- 5.3, p< 0.05)

Author, Year Country Patient Sample Size Provider Sample Size Practice Sample Size	KQ5 outcomes: Intermediate outcomes, improved knowledge, improved shared decision making	KQ6 outcomes: Adverse effects of the strategy, such as increased time burden on clinicians, sustainability, diagnostic resource use associated with POC testing, diagnostic coding	Comments
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)			
Wutzke, 2007 Australia Patient N = 12,217 Provider N = 5,758 Practice N = NR	Proportion of the community reporting certain behaviors are appropriate for cold and flu Pre 2002 % appropriate vs. Post 2002 % appropriate (change, p) vs. Post 2003 % appropriate (change, p) vs. Post 2004 % appropriate (change, p) Get some rest: 89.4 vs. 89.7 (+ 0.3, NS) vs. 90.8 (+ 1.4, NS) vs. 91.1 (+ 1.7, NS) Drink lots of fluids: 96.4 vs. 97.8 (+ 1.4, NS) vs. 97.3 (+ 0.9, NS) vs. 97.3 (+ 0.9, NS) Take antibiotics: 28.7 vs. 24.9 (- 3.8, NS) vs. 26.1 (- 2.6, NS) vs. 21.7 (- 7.0, p<0.05; 95% CI, 3.5 to 10.5	NR	

[a]Median adult and pediatric ARIs per practice multiplied by number of practices

[b]Median providers per practice multiplied by number of practices

Please see Appendix B, Included Studies, for full study references.

Appendix G. Quality Assessment of Observational Studies

Quality (Risk of Bias) Assessment of Individual Studies

Determination of Ratings

Studies that had a serious flaw were rated poor in quality, studies that met all criteria were rated good in quality, and the remainder of the studies were rated fair in quality. As the fair quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair quality studies are likely to be valid, while others are only possibly valid. A poor quality study is not valid as the results are at least as likely to reflect flaws in the study design as a true difference between the compared interventions. A serious flaw is reflected by failure to meet combinations of items on the quality assessment checklist; for example, unclear randomization and allocation concealment methods combined with differences between randomized groups at baseline in potentially prognostic characteristics and either high attrition or lack of an intention to treat analysis. Quality assessments of studies included in this review are included in the following evidence tables.

Note Regarding Evidence Table

Quality assessments for each included study are contained in separate rows of the evidence table (included below). Evidence rows for each study span multiple pages of this appendix document. Each study is identified in the first column of the evidence table.

Evidence Table G1. Quality assessment of observational studies

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)				
Bjerrum, 2004	Unclear	Overall: Unclear* Differential: Unclear*	Yes	Yes
Bjerrum, 2006	Unclear: All 52 participating providers were invited and agreed to participate, but method for allocating to intervention vs. control group NR.	Unclear whether all GPs enrolled completed study. Data collected for control providers only in second time period.	Yes: antibiotics identified by WHO classification code	Yes: treatment given reported by provider using published Audit Project Odense method, citation given

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Bjerrum, 2011	Unclear: providers invited to participate, selection criteria NR; results presented only for providers completing both registrations	Unclear: results presented only for providers participating in both registration periods, participation rates could be different before and after intervention (i.e. for comparison groups)	No: unclear how antibiotic prescribing and classification were defined	Yes: self-registry by GP during consultation, APO citation given
Blaschke, 2014	No: comparison groups defined based on whether or not RIDT was used and influenza diagnosed in the ED visit, and not clear that analysis adjusted for other factors that could affect outcomes	No (NA): cross-sectional	Yes, though no classification reported for antibiotics	Yes: used data from National Hospital Ambulatory Medical Care Survey (NHAMCS), an annual survey of US ED visits conducted by the National Center for Health Statistics and the CDC

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Ashe, 2006 (Please refer to Vodicka, 2013 systematic review)					
Bjerrum, 2004	Unclear	Yes	NA	Fair	* Number of clinicians enrolled or possibly lost to followup in the prospective registration of patients is not clearly reported
Bjerrum, 2006	Unclear: outcomes recorded by providers with no blinding	Yes: "we used 95% confidence intervals (CI) adjusted for clustering of data according to practices." Antibiotic prescribing outcomes also reported stratified by site of infection.	Yes: data collected over 3-week periods in two consecutive winter seasons	Fair	
Bjerrum, 2011	Unclear: outcomes recorded by providers with no blinding	Yes: "we used 95% confidence intervals (CI) adjusted for clustering to GPs." Antibiotic prescribing outcomes also reported stratified by country	Yes: data collected over 3-week periods in two consecutive winter seasons	Fair	Happy Audit study
Blaschke, 2014	Unclear: used data from an independent national survey database, hospital staff collect data with training from Census Bureau, ICD-9 codes used for diagnoses, data "reviewed for completeness and accuracy and validated by representatives from the NCHS." However, methods for extracting study data from database and whether study personnel were blinded is not reported.	Unclear: Outcomes compared as percent differences across 3 groups defined by RIDT use and flu diagnosis; paper does not report any adjustment of these percent differences for factors likely affecting outcomes, though weights based on sampling design (including geographic region, hospital, ED) appear to be used in calculating CIs	NA: cross-sectional design	Fair	ICD-9 codes for influenza lack specificity. I suspect the PPV of such codes is poor

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Bush 1979 (Please refer to Boonacker, 2010 systematic review)				
Chowdhury, 2007	Yes	No: antibiotic prescribing outcome reported for all 24 THCs	Unclear	No for outcomes: only that "prescribing data was collected from THCs records." Yes for exposure
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)				
Gonzales, 1999 Gonzales, 2001	Yes	No	Yes	Yes
Gonzales, 2004 Gonzales, 2005	Yes	No	Yes	Yes
Gonzales, 2008	Yes	No	Yes	Yes
Harris, 2003	Unclear	No	Yes	No
Hemo, 2009	Yes	No	Yes	Yes
Herman, 2009 (Please refer to Andrews, 2012 systematic review)				
Holloway, 2009	Yes: four districts studied (of 75 total in Nepal), 2/4 districts randomly assigned to intervention (method NR); sites within districts, villages within sites, and households within villages randomly selected for data collection	No: four districts studied before and after intervention, loss to FU NR. Individual patients not followed longitudinally.	Yes: treatment information collected through household interviews	Yes for both exposures and outcomes. Diagnoses/ARI severity from survey responses validated against health workers' diagnoses in baseline study.

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Bush 1979 (Please refer to Boonacker, 2010 systematic review)					
Chowdhury, 2007	Unclear	Yes: study restricted to clinics with high baseline use, with further matching of intervention and control groups by baseline use, methods for matching NR	Unclear	Fair	
Francis, 2006 (Please refer to Vodicka, 2013 systematic review)					
Gonzales, 1999 Gonzales, 2001	Unclear	Yes	Yes	Fair	
Gonzales, 2004 Gonzales, 2005	Yes	Yes	Yes	Fair	
Gonzales, 2008	Yes	Yes	Yes	Good	Would have liked a comment about any "epidemics" like influenza which occurred in the comparison and control group areas
Harris, 2003	Unclear	Yes	Yes	Fair	
Hemo, 2009	Yes	Yes	Yes	Good	
Herman, 2009 (Please refer to Andrews, 2012 systematic review)					
Holloway, 2009	Unclear: trained research staff used survey instrument validated for diagnosis, though no validation reported for treatments and blinding NR.	Yes: analysis includes ARI severity, time (pre/post), and intervention status	Yes: treatment outcomes, with winter season after intervention compared to winter season before.	Fair	

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)				
Little, 2014	Yes; simple clinical proforma used to create a large generalizable prospective cohort; negligible barriers to recruitment	No (overall); No (differential)	Yes: all studies within the main DESCARTE study had same outcome measures; complications was main outcome measure	Yes: review of patient notes with a standardized proforma (separated into terms showing possible consultation diagnosis or symptom presentation)
Litvin, 2013	No: intervention clinics volunteered to participate	No: one of 9 practices (11%) closed and withdrew (data included through 7/1/11)	Yes, with algorithms incorporating text strings and ICD-9 codes to define diagnoses, and CDC guidelines to define appropriate treatment by diagnosis	Yes for both exposures and outcomes.
Llor, 2011	Unclear: intervention and control providers were from different communities, not further described	Unclear: results presented only for providers participating in both registration periods (intervention groups), and control providers participated in second registration period only.	No: unclear how antibiotic prescribing and classification were defined	Yes: self-registry by GP during consultation, APO citation given
Llor, 2012	Unclear: not described in this paper but in other Happy Audit studies intervention and control providers were from different communities, not further described	Unclear whether results for intervention groups presented only for providers participating in both registration periods, but this was true in other Happy Audit studies. Control providers participated in second registration period only.	No: unclear how antibiotic prescribing defined	Yes: self-registry by GP during consultation, APO citation given
Llor, 2012	Unclear: intervention and control providers were from different communities, not further described	Unclear whether results for intervention groups presented only for providers participating in both registration periods, but this was true in other Happy Audit studies. Control providers participated in second registration period only.	No: unclear how antibiotic prescribing defined	Yes: self-registry by GP during consultation, APO citation given

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Isaacman, 1992 (Please refer to Andrews, 2012 systematic review)					
Little, 2014	Yes: outcome assessors (reviewers) blinded to aim of study (assessing affect of antibiotic prescription strategies)	Yes: log reg accounting for clustering by GP, controlling for case report form variables	Yes: duration of followup 4 weeks	Good	
Litvin, 2013	Unclear: blinding and database validation NR	Yes: longitudinal models included time and "random practice effects". Practice-level observations weighted by "practices' numbers of ARI encounters during the quarter."	Yes: intervention conducted in two phases over 27 months, with ARI treatment outcomes	Fair	
Llor, 2011	Unclear: outcomes recorded by providers with no blinding	Yes: regression model adjusted for use of RADTs, age, gender, presenting signs, diagnosis, and patient demand for antibiotics.	Yes: data collected over 3-week periods in two consecutive winter seasons	Fair	Happy Audit study
Llor, 2012	Unclear: outcomes recorded by providers with no blinding	Yes: regression model adjusted for use/results of CRP, age, gender, presenting symptoms/ signs, diagnosis, radiography, and patient demand for antibiotics	Yes: data collected in two consecutive winter seasons	Fair	Happy Audit study
Llor, 2012	Unclear: outcomes recorded by providers with no blinding	Yes: regression model adjusted for use/results of CRP, age, gender, comorbidity, presenting signs, duration of symptoms, diagnosis, radiography, and patient demand for antibiotics	Yes: data collected over 3-week periods in two consecutive winter seasons	Fair	Happy Audit study

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Llor, 2014	No: two intervention groups were from different communities, not further described; before/after results presented only for providers completing both registrations	No overall: 9.6% loss to followup. Yes for differential: 6.3% withdrew from one intervention group, 18% from the other	Yes: registration template shown with specific antibiotics listed	Yes: self-registry by GP during consultation, APO citation given, template shown
Mainous, 2013	No: intervention clinics volunteered to participate in response to email to Practice Partner Research Network members; other PPRNet practices used as controls. No inclusion/exclusion criteria or excluded practices reported.	No: Loss to FU NR, but both intervention and control clinics belonged to an existing research network (PPRNet) with common EHR and quarterly data pooling	Yes, with algorithms incorporating text strings and ICD-9 codes to define diagnoses, and CDC guidelines to define appropriate treatment by diagnosis	Yes for both exposures and outcomes
Maor, 2011 (Please refer to Andrews, 2012 systematic review)				
McKay, 2011	Unclear	No	No	No
McNulty, 2010	Yes	No	Yes	Yes
Perz, 2002	Unclear: intervention in one urban county, and the 3 other major urban counties in the state were controls. However, there were large baseline demographic differences (27% black in intervention county, range 54 to 90% in 3 control counties).	No: data reported for all 3 control counties (combined)	Yes, though antibiotic prescriptions not linked with individual visits and diagnoses: "prescriptions included were those filled for antimicrobial drugs administered orally and typically used for treatment of respiratory infections in pediatric outpatients." Outpatient visits for a diagnosed respiratory illness were a separate, secondary outcome (ICD-9 codes used).	Yes

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Llor, 2014	Unclear: outcomes recorded by providers with no blinding	Yes: regression model adjusted for age, gender, signs and symptoms, referral, antibiotic demand, and "burden of GPs."	Yes: data collected in winter 2008 and early 2009	Fair	Happy Audit study
Mainous, 2013	Unclear: blinding and database validation NR	Yes: Control clinics matched to intervention clinics for number of providers and baseline ARIs. Statistical adjustment for time, practice size and specialty, region, and baseline ARIs.	Yes: 15 months after intervention, with ARI treatment outcomes	Fair	
Maor, 2011 (Please refer to Andrews, 2012 systematic review)					
McKay, 2011	Unclear	Time trends for use of antibiotics only	Yes	Fair	
McNulty, 2010	unclear	Yes	Yes	Fair	
Perz, 2002	Unclear: validation of TennCare database and blinding NR	Yes: regression models for prescription rates adjusted for county, age, race, study year; antibiotic resistance stratified by study year and antibiotic category	Yes: 12 months after intervention, prescribing and resistance outcomes	Fair	

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Rattinger, 2012	Unclear: process for selecting the two VA health centers not described, and they were in different states (Maryland and Utah). There were large baseline differences in race and marital status, but outcomes were adjusted for these variables. For individual visits, exclusion criteria and numbers excluded were reported.	No: one intervention and one control site studied before and after intervention. Individual patients not followed longitudinally.	Yes, with algorithms incorporating text strings to define diagnoses, and CDC guidelines to define appropriate treatment by diagnosis	Yes: visits identified by automated case-finding algorithm and data for these visits then manually abstracted.
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)				
Reyes-Morales, 2009	Unclear: process for selecting clinics not described, though intervention and control clinics reported to be similar. Both intervention and control physicians "agreed to participate." Average three patients per physician analyzed at each stage, but how they were selected NR (all gave consent to participate).	No: outcomes reported for all 106 participating physicians	Yes	Yes

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Rattinger, 2012	Unclear: cases identified by automated algorithm, but data from these visits manually abstracted and blinding NR	Yes: regression models adjusted for age, marital status, sex, and race/ethnicity	Yes: 4 years from start of intervention, prescribing outcomes	Fair	
Razon, 2005 (Please refer to Vodicka, 2013 systematic review)					
Reyes-Morales, 2009	Yes: some patient and physician data by self-report, but corroborated by record and prescription review and "Data were collected by previously trained nurses who were blinded to the hypothesis of the study and unaware of the intervention."	Unclear: intervention and control clinics similar in locations, number of physicians, infrastructure, and population served, but not clear if this resulted from a matching procedure. In addition, "the intervention effect was calculated by using the differences-in-differences model, adjusting for cluster sampling of physicians," but no further explanation of this adjustment or discussion of adjustment for other confounders.	Unclear: 7 months including 3-month intervention, baseline, and followup evaluations; season NR	Fair	

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Rubin, 2005	No: community selected because of baseline high frequency of cephalosporin use in children. For Medicaid data, "the rest of rural Utah" used as comparator, and there were baseline differences in antibiotic use between community and state (e.g. proportion of nonstrep pharyngitis treated with antibiotics: 95% vs. 65%). One of the few providers in Community A also declined to participate in study.	No: FU not specifically reported, but Medicaid claims data used for both baseline and intervention period, and manual chart review was done for URTI episodes in each period with comparable N's to Medicaid data.	Yes, with ICD-9 codes used to identify URTI episodes from charts and Medicaid claims	Yes
Siegel, 2006	No: 17 of 30 practitioners in a pediatric Practice-Based Research Network compared with 30 "randomly selected community pediatricians," of whom 12 (40%) did not respond. Selection method NR for PBRN providers.	No: data on prescribing practices collected retrospectively using questionnaires mailed to providers, so no loss to FU	Yes (antibiotic prescribing, SNAP use)	Yes: provider questionnaire reproduced in publication
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)				
Smeets, 2009	No: 25 groups of GPs agreed to participate (out of 84 invited groups)	No: enrolled groups N= 141, at analysis, Intervention N=131, C= 127	Yes, RX claims data obtained from a regional health insurance company database	Yes

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Rubin, 2005	Unclear: two data sources for patient-level data, Medicaid claims and chart review (no linking of these data sources reported), but blinding NR.	Yes: models for patient-level data included community, time, diagnosis and antimicrobial class, but not baseline antibiotic use which differed between groups	Unclear: followup data collected during the same period intervention was conducted, which was from January through June when URTI season likely ending	Poor	
Siegel, 2006	No: questionnaire asked providers to retrospectively estimate antibiotic prescribing and SNAP use at several timepoints before and after Otitis Media Study. Recall bias likely, as only PBRN providers participated in study.	Yes: outcomes for the two provider groups were compared before and after the SNAP intervention (i.e. minimal adjustment for time)	Yes: questionnaire covers 4-year period	Poor	
Smabrekke, 2002 (Please refer to Boonacker, 2010 and Vodicka, 2013 systematic reviews)					
Smeets, 2009	Yes	Unclear	Yes	Fair	

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Strandberg, 2005	No: all 80 general practitioners at 14 public health centers invited to participate in audit; 45 who agreed were intervention group, 35 others were control group. Baseline differences in prescribing patterns between groups. 12 private GPs excluded.	Unclear: 4/45 participants (8.8%) and 5/35 nonparticipants (14%) were missing data at final followup. Considering all 5 time periods, data were missing for 2% of participating providers (4/225) and 19% of nonparticipants (33/175). Authors identify only "dropout of one and two GPs, respectively, because they had no registered patients during one of the periods."	Unclear: broad vs. narrow-spectrum antibiotics and appropriate use not clearly defined	No: unclear how 1998 data extract on diagnoses and treatments related to 1994/1995 study period data collection, or how diagnoses were defined in and extracted from electronic records.
Trepka, 2001	Unclear: intervention and control groups in different geographical regions of Wisconsin (north vs. central). Within these regions, households randomly selected for outcome surveys; 4.7% refused and 36% had no phone or could not be reached. No statistically significant difference in refusal rates between regions, but rates of those not reached NR by intervention group. However, baseline knowledge outcomes similar between regions.	No: 65/430 (15%) of respondents lost to FU overall, 18% in intervention and 13% in control areas. Analyses were restricted to parents completing both surveys.	Yes	Yes

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Strandberg, 2005	Unclear: data extraction method NR (automated vs. manual), no blinding or database validation reported	No: stratified time series analysis only: results reported for each of five time periods, but no adjustment for other confounders, including baseline prescribing patterns which differed between participants and nonparticipants	Unclear: 3 months after registration intervention	Poor	
Trepka, 2001	Unclear: blinding and questionnaire validation NR	Yes: cofactors associated with knowledge outcomes in univariate analysis ($p<0.1$) were entered into multivariate models, though univariate results also reported	Yes: knowledge outcome, follow up survey one year after baseline survey and 9 months after intervention began	Fair	

Author, Year	Nonbiased selection?	High overall loss to followup or differential loss to followup?	Outcomes prespecified and defined?	Ascertainment techniques adequately described?
Vinnard, 2013	No: for AD study, intervention groups defined by high baseline antibiotic use. In PM study, there were large baseline differences in antibiotic use reported. In both groups, intervention providers were selected from university faculty (CPUP), and control group were nonfaculty providers (CCA).	No: results reported for all 28 providers in AD study; for PM study, results reported for *more* providers than described in methods (70 vs. 40)	Yes	Yes: research staff abstracted antibiotic data from medical records using structured abstraction form
Weiss, 2011	Yes, database	No (NA): no patient-level data	Yes	Yes
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)				
Wutzke, 2007	Yes	Unclear	Yes	Yes

Author, Year	Nonbiased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of followup?	Overall quality rating	Comments
Vinnard, 2013	Unclear: no blinding reported for outcomes assessors	Yes: intervention and control providers matched for baseline bronchitis visits. Models of effects of intervention on antibiotic prescribing included provider, time, and a time/intervention interaction term. AD model also adjusted for sex and smoking	Yes: one year for AD study, two years for PM study	Fair	Two substudies included: academic detailing (AD) and patient mailing (PM) Clinical Practices of the University of Pennsylvania (CPUP) practice providers are university faculty; Clinical Care Associates (CCA) providers are nonfaculty but affiliated with the university
Weiss, 2011	Unclear	Unclear: model variables not provided; time trends for antibiotic prescriptions filled	Yes	Fair	
Wheeler, 2001 (Please refer to Andrews, 2012 systematic review)					
Wutzke, 2007	Yes	Unclear: population surveys were weighted by age and gender, provider surveys not adjusted or weighted, drug utilization data adjusted for seasonality and timing of the initial intervention	Yes	Fair	

Please see Appendix B. Included Studies for full study references.

Appendix H. Data Abstraction of Systematic Reviews

Note Regarding Evidence Table

Data abstractions for each included study are contained in separate rows of the evidence table (included below). Evidence rows for each study span multiple pages of this appendix document. Each study is identified in the first column of the evidence table.

Evidence Table H1. Data abstraction of systematic reviews

Author, Year Country	Aims	Timeperiod Covered	Eligibility Criteria
Aabenhus, 2014 Denmark	To assess the benefits and harms of point-of-care biomarker tests of infection to guide antibiotic treatment in patients presenting with symptoms of acute respiratory infections in primary care settings regardless of age.	Through January 2014	Study Designs: Randomized controlled trials (RCTs) and cluster-RCTs in primary care. Participants: Patients of all ages defined as having ARIs. Interventions: (1) Point-of-care biomarkers including C-reactive protein, procalcitonin and white blood cell count. Excluded Strep A test or Monospot. (2) Standard of care. Outcome Measures: Primary (1) Number of patients given an antibiotic prescription at the index consultation and at 28 days followup. (2) Number of patients with substantial improvement (including full recovery) at day seven. (3) Total mortality at 28 days followup. Secondary (1) Number of patients in need of a reconsultation at 28 days followup. (2) Number of patients in need of a hospital admission at 28 days followup. (3) Duration of the ARI (e.g. mean or median days with restrictions in daily activities due to the infection). (4) Number of satisfied patients. (5) Number of patients with substantial improvement (including full recovery) at 28 days followup.

Author, Year Country	Number of Participants	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Aabenhus, 2014 Denmark	3,284	RCTs studying the treatment of ARIs with the C-reactive protein point-of-care test versus the standard of care.	Adults and children with: (1) Cough (2) Discolored/increased sputum (3) Fever (4) Runny nose (5) Respiratory distress (6) Feeling unwell (7) Combinations of focal and systemic symptoms having a duration of less than four weeks Diagnoses included: (1) Lower or upper respiratory tract infection (2) Pneumonia (3) Bronchitis (4) Acute exacerbations of chronic obstructive pulmonary disease or asthma (5) Pharyngitis (6) Tonsillitis (7) Laryngitis (8) Rhinosinusitis, (9) Common cold (10) Acute otitis media (11) Influenza	(1) Point-of-care test vs. the standard of care (no point-of-care test) *The only point-of-care biomarker of infection available to primary care at the time of this review was C-reactive protein.

Author, Year Country	Main Results	Adverse Events
Aabenhus, 2014 Denmark	KQ 1: A reduction in the use of antibiotic treatments was found in the C-reactive protein group (631/1685) versus standard of care (785/1599). The pooled result showed a statistically significant effect of C-reactive protein testing on the number of antibiotic prescriptions issued in primary care settings for ARIs, RR: 0.78, 95% CI: 0.66 to 0.92. Appropriateness of antibiotic prescribing and use NR/not defined. KQ 2: NR KQ 3: No deaths or serious complications were reported in any of the studies. Five of the six studies reported that there had been no hospitalizations in the followup period, 30 hospitalizations in the C-reactive protein group reported in Little 2013, 15 cases reviewed: cardiac (two); respiratory (eight), generally unwell/fever (two); gastrointestinal symptoms (two); sinusitis (one). All hospitalizations may not have been directly related to the intervention. KQ 4: Patient satisfaction: Detected no differences. However, unable to draw clear conclusions as only 2 of the included studies reported this outcome. Reconsultation rates: There were no significant differences in reconsultation rates. Patient symptoms: No difference between using a C-reactive protein point-of-care test and standard care in clinical recovery (defined as at least substantial improvement at day 7 and 28 or need for re-consultations day 28). No differences were observed in patient-reported measures (e.g. mean or median days with restrictions in daily activities due to the infection). KQ 5: NR	KQ 6: NR

Author, Year Country	Aims	Timeperiod Covered	Eligibility Criteria
Doan, 2014 Canada	Determine if the use of a rapid viral detection test for children with an ARI in EDs changes patient management and resource use (including precautionary testing, antibiotic use, and length of visit) in the ED, compared with not using a rapid viral detection test	Through December 2011	Study Designs: RCTs evaluating the use of rapid viral diagnosis in children admitted to the ED with an ARI Participants: (1) Studies of otherwise healthy children aged 0-18 years old (2) Studies which reported separately on subgroups of children under 18 years of age, admitted to an ED with a clinical presentation consistent with ARI (fever and respiratory symptoms such as cough, runny nose, sore throat, or congested nose) Interventions: Rapid viral diagnosis from nasal pharyngeal aspirates or swabs by direct or indirect immunofluorescent test, enzyme immunoassays, optical immunoassay, or molecular testing such as multiplex polymerase chain reaction. Results are made available during the participants' stay in the ED Outcome Measures Primary Outcomes: (1) Antimicrobial prescription rate in the ED (reduction of antibiotic use by 25% [RR=0.75] as clinically important) Secondary Outcomes: (1) Length of ED stay (reduction of 30 minutes considered clinically important) (2) Rate of ancillary tests (any blood tests or chest imaging or urine investigations) requested (reduction in ancillary testing of 25% [RR=0.75] considered clinically important) (3) Rate of physician visit (ED or office) within 2 weeks after discharged from ED (relative increase in physician visit within 2 weeks of discharge from an ED or 10% [RR=1.10] considered clinically important)
Doan, 2014 Canada Continued.			(4) Hospital admission rate (reduction in admission rate of 25% [RR=0.75] considered clinically important) (5) Acceptability of nasal specimen collection sampling for rapid viral testing (discomfort level with invasiveness of the procedure)

Author, Year Country	Number of Participants	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Doan, 2014 Canada	1,588 (759 in rapid viral testing group, 829 in control group)	Three RCTs and one quasi-RCT were included	Bonner 2003: Previously healthy participants, age 2 months to 21 years old, presenting to ED with fever, respiratory symptoms, malaise, or headaches of ≤ 72 hours duration Poehling 2006: children < 5 years old presenting to ED with fever or acute respiratory symptoms during the 2002-2003 and 2003-2004 influenza seasons Iyer 2006: children 2 to 24 months of age presenting to ED with fever Doan 2009: previously healthy children age 3 to 36 months old presenting to ED with fever and any respiratory symptoms	Bonner 2003: Treatment: results of nasopharyngeal swab for rapid influenza testing using FluOIA test (turnaround time < 25 minutes) being revealed to treating physicians at initial patient assessment Control: results of the rapid test were not made available to the treating physicians Poehling 2006: Treatment: results of rapid influenza testing were made available to the treating physician prior to patient assessment Control: standard testing with results made unavailable until the subject had been discharged from the ED Iyer 2006: Treatment: nasal swab for rapid influenza testing (using Quickvue), providing a result within 30 minutes Control: nasal swab for rapid influenza testing (using Quickvue), but these were performed only twice daily to simulate routine laboratory testing turnaround, and results were not made available to the treating physician using the patient had been discharged from the ED
Doan, 2014 Canada Continued.				Doan 2009: Treatment: nasopharyngeal aspirate for rapid respiratory virus panel (influenza A/B, parainfluenza 1/2/3, RSV, Adenovirus) using direct immunofluorescence assay (Light Diagnostics SimulFluor Respiratory Screening agent) Control: routine admission to ED. Any test done was requested after assessment by treating physician

Author, Year Country	Main Results	Adverse Events
Doan, 2014 Canada	KQ 1: Antibiotics Prescribed in ED (Rapid Viral Testing vs. Control RR): RR=0.89; 95% CI, 0.71 to 1.12 Antibiotics Prescribed in ED, sensitivity analysis: 0.86 (0.61 to 1.22) KQ 2: NR KQ 3: NR KQ 4: Blood investigations (e.g. cell count and/or culture) (Rapid Viral Testing vs. Control RR): RR=0.79; 95% CI, 0.62 to1.00 Blood investigations, sensitivity analysis: 0.61 (0.42 to 0.89) Urine testing (Rapid Viral Testing vs. Control RR): RR=0.97; 95% CI, 0.79 to 1.19 Urine testing, sensitivity analysis: 0.93 (0.70 to 1.25) Chest radiography (Rapid Viral Testing vs. Control RR): RR=0.77; 95% CI, 0.65 to 0.91 Chest radiography, sensitivity analysis: 0.59 (0.43 to 0.81) Visits to physician or ED post ED discharge (Rapid Viral Testing vs. Control RR): RR=1.00; 95% CI, 0.77 to 1.29 KQ 5: NR	KQ 6: Mean ED length of visit in minutes (Rapid Viral Testing vs. Control, mean difference; 95% CI): -10.61; 95% CI, -22.47 to 1.25 Mean ED length of visit in minutes, sensitivity analysis: -19.47 (-51.38 to 12.44)
Doan, 2014 Canada Continued.		

Author, Year Country	Aims	Timeperiod Covered	Eligibility Criteria
Huang, 2013 China	To systematically review studies that have examined the association between POC C- reactive protein testing and antibiotic prescribing for RTIs in general practice	Through June 2013	Population and Interventions: Studies were included that examined patients who had been diagnosed with RTIs and compared the antibiotic prescribing rate of a POC CRP testing group with a no-POC CRP testing group Study Designs: RCTs (including parallel-group RCTs, cluster RCTs, crossover RCTs, and factorial RCTs) or observational studies

Author, Year Country	Number of Participants	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Huang, 2013 China	10,005 patients with RTIs	3 cluster RCTs, 4 parallel-group RCTs, and 6 observational studies	Included studies of populations from the Netherlands (4 studies), Norway (3 studies), Denmark (2 studies), Spain (2 studies), Ireland (1 study), and the US (1 study)	POC testing vs. no-POC testing

Author, Year Country	Main Results	Adverse Events
Huang, 2013 China	KQ 1: Antibiotic prescribing at the index consultation*: RR=0.75; 95% CI, 0.67 to 0.83 Antibiotic prescribing at any time during the 28-day followup period*: RR=0.85; 95% CI, 0.70 to 1.01 KQ 2: NR KQ 3: NR KQ 4: Patient satisfaction*: RR=1.07; 95% CI, 0.98 to 1.17 KQ 5: NR	KQ 6: NR

Author, Year Country	Aims	Timeperiod Covered	Eligibility Criteria
Schuetz, 2011 Schuetz, 2012 United States, Canada	Schuetz 2011: Summarize the evidence based on previous RCTs for using PCT measurement in respiratory infections and sepsis from the clinical settings for which the most RCT data are available, namely, primary care, the ED, the medical ICU, and the surgical ICU. Proposed clinical algorithms for use in future US trials Schuetz 2012: Assess the safety and efficacy of using procalcitonin for starting or stopping antibiotics over a large range of patients with varying severity of ARIs and from different clinical settings	Through 2011	Study Designs: Schuetz 2011: RCTs including adults with a diagnosis of respiratory tract infections (i.e. pneumonia, acute exacerbations of COPD, or other respiratory tract infections) or sepsis Schuetz 2012: RCTs of adult participants with ARIs who received an antibiotic treatment either based on a procalcitonin algorithm or usual care/guidelines Clinical Settings: Primary care, the ED, or the ICU Interventions: Measurement of PCT levels to inform decisions regarding antibiotic therapy (i.e. regarding its initiation and/or duration) Primary Endpoints: Schuetz 2012: all-cause mortality and treatment failure at 30 days Secondary Endpoints: Schuetz 2012: antibiotic use, length of hospital stay, length of ICU stay, number of days with restricted activities within 14 days after randomization

Author, Year Country	Number of Participants	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Schuetz, 2011 Schuetz, 2012 United States, Canada	4,221 total (2,610 in studies applicable to present review, e.g. primary care and select ED settings)	4 RCTs applicable to present review (2 multicenter noninferiority; 1 ED only, single center; 1 ED and inpatient multicenter)	Subjects with upper and lower RTI (2 studies) or CAP, AECOPD, bronchitis (2 studies)	Algorithm by PCT Level (µg/L) Primary care setting: <0.10, SRAA; 0.10-0.25, RAA; > 0.25, FRA; recheck PCT level at 6-24 hours if no antibiotics initiated; or <0.25, RAA; >0.25. RFA ED settings: <0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; recheck PCT level after 6-24 hours if no antibiotics initiated; or <0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; retest PCT level every 2 days; discontinue antibiotics with same cutoffs

Author, Year Country	Main Results	Adverse Events
Schuetz, 2011 Schuetz, 2012 United States, Canada	KQ 1: *Schuetz 2011* Briel 2008: Antibiotics Use, Control vs. PCT Prescription: 97% vs. 25% Duration (mean): 7.1 vs. 6.2 days Relative Reduction, % Prescription: -74 Duration: -13 Burkhardt 2010: Antibiotics Use, Control vs. PCT Prescription: 36.7% vs. 21.5% Duration (mean): 7.7 vs. 7.8 days Relative Reduction, % Prescription: -42 Duration: 1 *Schuetz 2012* PCT (n (%)) vs. Control (n (%)), Adjusted OR; 95% CI; p Initiation of antibiotics, Upper ARI: 43 (15) ED. 129 (48), OR=0.14; 95% CI, 0.09 to 0.22; p< 0.001 Initiation of antibiotics, Acute bronchitis: 61 (24) vs. 185 (66), OR=0.15; 95% CI, 0.10 to 0.23; p< 0.001 PCT (median (IQR)) vs. Control (median (IQR)), Adjusted OR; 95% CI; p Duration of antibiotics in days, Upper ARI: 7 (5 to 8) vs. 7 (6 to 7), OR=-1.16; 95% CI, -2.08 to -0.24; p=0.013 Total exposure of antibiotics in days, Upper ARI: 0 (0 to 0) vs. 0 (0 to 7), OR=-2.64; 95% CI, -3.16 to -2.11; p< 0.001 Duration of antibiotics in days, Acute bronchitis: 7 (4 to 9) vs. 7 (5 to 8), OR=-0.38; 95% CI, -1.21 to 0.46; p=0.375 Total exposure of antibiotics in days, Acute bronchitis: 0 (0 to 0) vs. 5 (0 to 7), OR=-3.06; 95% CI, -3.69 to -2.43; p< 0.001	KQ 6: NR

Author, Year Country	Aims	Timeperiod Covered	Eligibility Criteria
Schuetz, 2011 Schuetz, 2012 United States, Canada Continued.			
Spurling, 2013 Australia, United States	Evaluate use of delayed antibiotics compared with immediate or no antibiotics as a prescribing strategy for ARTIs	Through February 2013	Study Designs: Randomized controlled trials and open randomized trials Participants: Patients of all ages defined as having ARTIs Interventions: (1) Delayed antibiotic use defined as strategy involving use of or advice to use antibiotics more than 48 hours after initial consultation (2) Immediate antibiotic use defined as immediate use of prescription oral antibiotics given at initial consultation (3) No antibiotic use defined as no prescription of antibiotics at initial consultation Outcome Measures: Primary (1) Clinical outcomes for sore throat, AOM, bronchitis, common cold (2) Antibiotic use (3) Patient satisfaction (4) Antibiotic resistance Secondary (1) Adverse events of antibiotics (2) Complications of disease (3) Re-consultation (4) Use of alternative therapies

Author, Year Country	Number of Participants	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Schuetz, 2011 Schuetz, 2012 United States, Canada Continued.				
Spurling, 2013 Australia, United States	3,157	RCTs studying the treatment of ARTIs with delayed antibiotics versus immediate or no antibiotics	Adults and children with: (1) common cold or (2) cough or (3) sore throat or (4) cough and at least one symptom or sign localizing to lower respiratory tract Children with: (1) AOM or (2) sore throat	(1) Delayed antibiotics vs. immediate antibiotics (2) No antibiotics vs. delayed antibiotics (3) Delayed antibiotics vs. immediate antibiotics vs. no antibiotics

Author, Year Country	Main Results	Adverse Events
Schuetz, 2011 Schuetz, 2012 United States, Canada Continued.	KQ 2: NR KQ 3: *Schuetz 2011* PCT Algorithm vs. No PCT Algorithm, Total; Weight, %; Fixed, Peto OR; 95% CI Mortality in Primary Care Trials: 507 vs. 501, 0.3, OR=0.13; 95% CI, 0 to 6.64 *Schuetz 2012:* PCT (n (%)) vs. Control (n (%)), Adjusted OR; 95% CI; p Mortality, Upper ARI: 0 (0) vs. 1 (0.4); NR; NR Treatment failure, Upper ARI: 93 (33.0) vs. 92 (34.5), OR=0.95; 95% CI, 0.73 to 1.24; p=0.687 Mortality, Acute Bronchitis: 0 (0) vs. 2 (0.8); NR; NR KQ 4: *Schuetz 2012:* PCT (median (IQR)) vs. Control (median (IQR)), Adjusted OR; 95% CI; p Days with Restricted Activities: 9 (6 to 14) vs. 9 (5 to 14), OR=0.05; 95% CI, -0.46 to 0.56, p=0.854 KQ 5: NR	
Spurling, 2013 Australia, United States	KQ 1: Delayed antibiotics resulted in a significant reduction in antibiotic use compared with immediate antibiotics. A 'no antibiotics' strategy resulted in the least antibiotic use. Appropriateness of antibiotic prescribing and use NR/not defined. KQ 2: NR KQ 3: Minor differences in clinical AEs of antibiotics with no significant difference in complication rates. Antibiotic resistance: NR. KQ 4: Patient satisfaction Delayed vs. immediate antibiotics, OR; 95% CI: OR=0.52; 95% CI, 0.35 to 0.76 Overall 92% of participants in immediate antibiotics arms were satisfied vs. 87% in the delayed arms. Delayed vs. no antibiotics, OR; 95% CI: OR=1.44; 95% CI, 0.99 to 2.10 Reconsultation rates: no difference between immediate and delayed groups Patient symptoms: no difference between delayed, immediate, and no prescribed antibiotics for clinical outcomes evaluated in cough and common cold. In patients with AOM and sore throat, immediate antibiotics were more effective than delayed for fever, pain, and malaise in some studies. KQ 5: NR	KQ 6: NR

Please see Appendix B, Included Studies, for full study references.

Appendix I. Quality Assessment of Systematic Reviews

Quality (Risk of Bias) Assessment of Individual Studies

Determination of Ratings

Studies that had a serious flaw were rated poor in quality, studies that met all criteria were rated good in quality, and the remainder of the studies were rated fair in quality. As the fair quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair quality studies are likely to be valid, while others are only possibly valid. A poor quality study is not valid as the results are at least as likely to reflect flaws in the study design as a true difference between the compared interventions. A serious flaw is reflected by failure to meet combinations of items on the quality assessment checklist; for example, unclear randomization and allocation concealment methods combined with differences between randomized groups at baseline in potentially prognostic characteristics and either high attrition or lack of an intention to treat analysis. Quality assessments of studies included in this review are included in the following evidence tables.

Note Regarding Evidence Table

Quality assessments for each included study are contained in separate rows of the evidence table (included below). Evidence rows for each study span multiple pages of this appendix document. Each study is identified in the first column of the evidence table.

Table I1. Quality assessment of systematic reviews

Author Year Country	Report clear review question, state inclusion and exclusion criteria of primary studies?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?	Primary studies summarized appropriately?	Quality Rating
Aabenhus, 2014 Denmark	Yes	Yes	Yes	Yes	Yes	Good
Doan, 2014 Canada	Yes	Yes	Yes	Yes	Yes	Good
Huang, 2013 China	Yes	No: only used 2 sources (MEDLINE and Embase)	Yes	Yes	No: included two data sets from a single study in the meta-analysis	Poor
Schuetz, 2011 Schuetz, 2012 United States, Canada	Yes	Yes	Yes	Yes	Yes	Good
Spurling, 2013 Australia, United States	Yes	Yes	Yes	Yes	Yes	Good

Please see Appendix B, Included Studies, for full study references.

Appendix J. Strength of Evidence

Table J1. Strength of evidence

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
1. For patients with acute RTI and no clear indication for antibiotic treatment, what is the comparative effectiveness of particular strategies in improving the prescription or use of antibiotics compared with other strategies or standard care?								
Overall Antibiotic Prescribing or Use (versus usual care unless other comparison noted)								
Education Interventions								
Patient Education Interventions								
Clinic-based Interventions								
Children up to age 14								
Moderate	RCT: 2 (679)	Medium	Direct	Consistent	Precise	Not detected	None	Reduced overall prescribing: Pooled estimate = 0.39 (95% CI, 0.26 to 0.58)
Insufficient	Observational: 1 (720)	Low	Direct	Unknown	Imprecise	Not detected	None	No difference found in prescriptions for acute RTI (OR 0.76; 95% CI, 0.56 to 1.04)
Final Rating: Moderate								Reduced overall prescribing
Children ≤ 24 months; AOM: Low	RCT: 1 (499)	Low	Direct	Unknown	Precise	Not detected	None	No effect seen. Mean number of antibiotics prescribed per patient diagnosed with AOM 1.7 vs. 1.9 (p=0.23)
Public Campaigns								

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Adults: Low	Observational: 2 (N = 1,888 in 1 study, unclear number of adults in the other [total population N = 2,711,848 in post period])	Low	Direct	Consistent	Precise	Not detected	None	Public campaigns did not affect prescribing for acute RTI in adults (p=0.9 to 1.0)
Children: Low	Observational: 3 (N = 84,979 in 1 study, unclear # children in the other [total population N = 2,711,848 in post period])	Low	Direct	Consistent	Precise	Not detected	None	Public campaigns resulted in reduced prescribing for antibiotics to treat acute RTIs, particularly otitis media (OR 0.652; 95% CI, 0.591 to 0.718)
Clinician Targeted								
Low	RCT: 1 (75 providers)	Medium	Direct	Unknown	Imprecise	Not detected	None	Limited evidence from one RCT suggests no difference in prescribing for acute rhinosinusitis (difference 1.4%)
Low	Observational: 4 (68 providers and all in Quebec)	Medium	Direct	Consistent	Precise	Not detected	None	Small reductions in overall prescribing and reductions of 7 to 10% when targeting clinicians with high rate of prescribing, and no impact on prescribing for pharyngitis (+0.3%)
Final Rating: Low								Small reductions in overall prescribing for acute RTIs, upper RTI and AOM, but not acute sinusitis or pharyngitis

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Patient and Clinician Targeted								
Moderate	RCT: 5 (16 clinics + 2,374 providers, 22,540 patients)	Medium	Direct	Consistent	Precise	Not detected	None	Combined education programs resulted in small reductions: -6.5% to -9.5%
Low	Observational: 4 (2,889 patients + 123,944 patient-years, 1,500+ providers, and all in Australia)	Medium	Direct	Consistent	Precise	Not detected	None	Mean reduction in antibiotic prescriptions 8.2% (95% CI, 4.8% to 11.5%). Reductions in children 10% to 18%, more in younger children. Adults: mixed evidence for bronchitis, 9% to 13% for upper RTI. Minimal effect on pharyngitis, sinusitis.
Final Rating: Moderate								Overall: Small reductions in prescribing.
Communication Interventions								
Communication vs. Usual Care: Moderate	RCT: 5 (594/5,513)	Medium	Direct	Consistent	Precise	Not detected	None	Overall antibiotic prescribing: Each of 5 studies of 5 different communication interventions found the intervention to reduce relative risk (range 0.69 to 0.17) and absolute risk (differences from 9.2% to 26.1%).
Communication vs. Education: Low	RCT: 2 (30+/632)	Medium	Direct	Consistent	Imprecise	Not detected	None	Overall antibiotic prescribing: One study found communication intervention to have a larger reduction compared with control (RR 0.17; 95% CI, 0.03 to 0.93) than education compared with control (RR 0.40; 95% CI, 0.08 to 1.92). Second study found no significant difference between communication and education interventions (RR 0.86; 95% CI, 0.40 to 1.93).

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Communication vs. CRP Testing: Low	RCT: 2 (123/2,426)	Medium	Direct	Inconsistent	Imprecise	Not detected	None	Overall antibiotic prescribing: One of 2 studies found the use of a communication intervention to be statistically significantly associated with higher relative risk of prescription (RR 1.17; 95% CI, 1.05 to 1.31). The second study found no significant difference (RR 0.85; 95% CI, 0.58 to 1.25).
Clinical Interventions								
Delayed Prescribing Strategies								
Delayed vs. Immediate Prescription: Moderate	RCT: 6 (1,664)	Medium	Direct	Consistent	Precise	Not detected	None	Reduced overall prescribing: OR's ranged from 0.00 (95% CI, 0.02 to 0.08) to 0.20 (95% CI, 0.09 to 0.44)
Different Delaying Strategies: Giving prescription with instructions vs. post-dating: Low	RCT: 2 (339)	Medium	Direct	Consistent	Imprecise	Not detected	None	No differences: 41% vs. 40% (OR 1.05; 95% CI, 0.68 to 1.62)
Different delaying strategies: Giving prescription with instructions vs. leaving for collection or recontacting: Low	RCT: 1 (319)	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference: OR 1.32 (95% CI, 0.68 to 2.58); OR 1.11 (95% CI, 0.58 to 2.11)
Decision Rules								
Overall prescriptions: Insufficient	RCT: 1 (20)	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference: 55% vs. 58%; p=NS
Clinical Prediction Score vs. Delayed Prescribing								
Overall Antibiotic use (patient reported): Low	RCT: 1 (325)	Medium	Direct	Unknown	Imprecise	Not detected	None	Lower use in clinical score group: 37% vs 46%; RR 0.71; 95% CI, 0.50 to 0.95
C-Reactive Protein Point of Care Testing								
Moderate	RCT: 6 (491/6,197)	Medium	Direct	Consistent	Precise	Not detected	None	Overall antibiotic prescribing: The relative risk for prescribing at the index consultation was lower in the CRP group (RR 0.73; 95% CI, 0.60 to 0.90; I2=85%).
Low	Observational: 1 (367/1,444)	Medium	Direct	Unknown	Precise	Not detected	None	Overall antibiotic prescribing: Adjusted OR = 0.43 (95% CI, 0.33 to 0.58)

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Final Rating: Moderate								Overall prescribing significantly reduced with CRP testing.
CRP with Clinical Algorithm vs. Clinical Algorithm Alone Low	RCT: 1 (1/131)	Medium	Direct	Unknown	Imprecise	Not detected	None	Overall antibiotic prescribing: One study found no difference between the use of POC CRP testing with a clinical algorithm to guide chest x-ray and antibiotic treatment and use of the clinical algorithm alone (RR 1.23; 95% CI, 0.77 to 2.00).
Procalcitonin Point of Care Testing								
Adults: Moderate	RCT: 5 SR: 2 (2,820)	Medium	Direct	Consistent	Precise	Not detected	None	Reduced prescribing in upper RTI (OR 0.14; 95% CI, 0.09 to 0.22), acute bronchitis (OR 0.15; 95% CI, 0.10 to 0.23), primary care (OR 0.1; 95% CI, 0.07 to 0.14)
Children: Low	RCT: 1 (337)	Low	Direct	Unknown	Precise	Not detected	None	Increased prescribing with procalcitonin (+ 21.7%; RR 4.34; 95% CI, 2.40 to 7.84)
Rapid Strep Point of Care Testing								
Overall prescribing: Moderate	RCT: 3 (1,896)	Medium	Direct	Consistent	Precise	Not detected	NA	Lower with use of a rapid strep test with a range of 20% to 52%
Rapid Viral Point of Care Testing								
Rapid Viral Testing vs. usual care in adults: Low	RCT: 1 (NR)	Medium	Direct	Unknown	Precise	Not detected	NA	Proportion of patients prescribed significantly lower in the patients assigned to point-of-care testing; 4.5% versus 12.3% (7.8% difference; p<0.01).
Rapid viral Testing vs. usual care in Children: Moderate	RCT: 4 (NR)	Medium	Direct	Consistent	Precise	Not detected	NA	No difference; Pooled estimate RR 0.89; 95% CI, 0.71 to 1.12 for overall prescribing
System-Level Interventions								
Electronic Decision Support with > 50% use of system: Moderate	RCT: 2 (240 clinicians)	Medium	Direct	Consistent	Precise	None	Rate of use = 57% and 100% (subgroup analysis)	Reduction of 9% with higher rates of use of system.

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Multifaceted Interventions								
Clinician education + audit/feedback: Low	RCT: 2 (Patient: 188,832, Provider: 251)	Medium	Direct	Inconsistent	Precise	Not detected	None	Difference not found: Range of absolute difference of differences (before to after) for intervention vs. control: -1.7% to 8.5%
Patient and Clinician Education plus Audit & Feedback: Low	Observational: 6 (Patient: 25,445; Provider: 690)	Medium	Direct	Consistent	Precise	Not detected	None	Difference of 24-26% for adults with bronchitis, no difference for older adults or children with pharyngitis.
Peer Academic Detailing (education, encouraging delayed prescribing, and audit & feedback): Insufficient	Observational: 1 (Patient N = NR Provider N = 382)	Medium	Direct	Unknown	Imprecise	Not detected	None	Small, nonsignificant reduction in prescribing (before vs after) Change: -1.29 (95% CI, -2.43 to -0.16)
Patient and Clinician Education plus Communication Training plus Audit & Feedback								
Low	RCT: 1 (Patient: 3,620 Provider: 89)	Medium	Direct	Unknown	Precise	Not detected	None	Reduced prescribing of antibiotics with interventions. Unadjusted: -12% (-18.9 to - 4.0) Adjusted: −10.7% (−20.3% to −1.0%)
Insufficient	Observational: 1 (Patient: NR Provider: 382)	Medium	Direct	Unknown	Precise	Not detected	None	No difference – both groups increased
Overall: Low								Overall: Small reduction in prescribing
Augmentation Interventions								
Delayed + Education: Insufficient	RCTs: 2 (Patients: 1,066)	Medium	Direct	Inconsistent	Precise	None	None	Inconsistent findings.
Point of Care Tests Combined with Other Strategies								
CRP + provider-focused communication vs. usual care and vs. communication alone: Moderate	RCT: 2 (Combo vs. usual: 2,269 and vs. communication: 2,533)	Medium	Direct	Consistent	Precise	Not detected	None	Reduced overall prescribing: EPC-calculated pooled OR (95% CI) for combo vs. usual = 0.30 (0.26 to 0.36) and vs. communication alone = 0.67 (0.56 to 0.78)

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
CRP + provider-focused communication CRP: Moderate for URTI/LRTI, Low for LRTI alone	RCT: 1 for upper/lower (2,224), 1 for lower alone (227)	Medium	Direct	Unknown	Precise for URTI/ LRTI and imprecise for LRTI alone	Not detected	None	Reduced overall prescribing for LRTI alone/face-to-face training = 0.47 (0.25 to 0.86) EPC-calculated OR (95% CI) for but not for upper/lower RTI-internet-based training = 0.87 (0.72 to 1.04)
Provider/patient education + CRP vs. usual: Low	Observational: 4 (10,312)	Medium	Direct	Consistent	Imprecise for rhinosinusitis, ears, tonsils, sinuses	Not detected	None	Reduced overall prescribing (Range of OR's) for: Sinusitis: 0.12 to 0.61 Bronchitis: 0.18 to 0.34 Pharyngitis: 0.23 to 0.40 Increased prescribing for infections of ears: OR 2.17 (1.06 to 4.49)
Provider/patient education + CRP vs. Provider/patient education alone Low	Observational: 3 (6,176)	Medium	Direct	Consistent	Imprecise	Not detected	None	Reduced overall prescribing OR (95% CI): 0.27 (0.15 to 0.49) Rhinosinusitis 0.63 (0.49-0.80 Bronchitis 0.32 (0.28-0.37) Pharyngitis
Rapid strep testing + clinical score vs. clinical score alone: Moderate	RCT: 2 (1,130)	Medium	Direct	Consistent	Imprecise	Not detected	None	Reduced overall prescribing; Pooled rates: 36% vs. 47%; EPC-calculated pooled OR 0.70 (95% CI, 0.50 to 0.98)
Rapid strep testing + decision rule vs. Rapid strep testing alone or usual care: Low	RCT: 1 (533)	Medium	Direct	Unknown	Imprecise	Not detected	None	Reduced overall prescribing 38% vs. 27% (RR 1.43; 95% CI, 0.98 to 2.11) vs. 58% (RR 0.66; 95% CI, 0.49 to 0.86)
Rapid strep testing + clinical score vs. delayed prescribing: Low	RCT: 1 (328)	Medium	Direct	Consistent	Imprecise	Not detected	None	Reduced overall prescribing 35% vs. 46%; RR 0.73 (95% CI, 0.52 to 0.98)
Appropriate Antibiotic Prescribing or Use (as defined by studies)								
Education Interventions								
Patient Education Interventions								
Clinic-based Interventions								
Adults with acute RTI: Low	RCT: 1 (968)	Medium	Direct	Unknown	Precise	Not detected	None	Reduced appropriate prescriptions: Adjusted absolute difference -19.7%; 95% CI, -5.8 to -33.04 based on ICD-9 codes
Public Campaigns								
Patient and Clinician Targeted								

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Moderate	RCT: 2 (Children: 1,016, Adults: 954)	Medium	Direct	Consistent	Precise	Not detected	None	Based on duration of symptoms, reduced inappropriate prescribing by 10.4% in pharyngitis (OR 0.6; 95% CI, 0.54-0.75); Based on ICD-9 codes, adjusted absolute difference -19.7% (95% CI, -5.8 to -33.04).
Insufficient	Observational: 1 (Patient: 1,177 Provider: 13)	Medium	Direct	Unknown	Precise	Not detected	None	Improved appropriate prescribing in sinusitis by 27% (p<0.001)
Final rating: Moderate								Improved prescribing in pharyngitis in children and acute RTI in adults
Communication Interventions								
Communication vs. Education: Low	RCT: 1 (30/552)	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference in appropriate antibiotic prescribing according to guidelines adapted by investigators (adjusted OR 1.03; 95% CI, 0.30 to 3.09)
Clinical Interventions								
Tympanometry Point of Care Testing								
Children: Low	RCT: 1 (398)	Medium	Direct	Unknown	Precise	Not detected	None	No, tympanometry did not impact prescribing (28.8% with tympanometry vs. 26.8% without; p=0.62)
Rapid Strep Point of Care Testing								
Appropriate prescribing: Low	RCT:1 (543)	Medium	Direct	Unknown	Precise	Not detected	NA	Reduced inappropriate antibiotic prescribing according to culture: 26.9% vs. 60.0%; p<0.001
System-Level Interventions								
Appropriate prescribing: Moderate	RCT: 2 (12,195)	Medium	Direct	Consistent	Precise	Not detected	Low adoption of intervention tools across studies	Difference between groups: 13% bronchitis, p=0.01; 24% AOM
Multifaceted Interventions								
Clinician Education plus a Clinical Algorithm: Insufficient	Observational: 1 (Patient: 1,495; Provider: 145)	High	Direct	Unknown	Precise	Not detected	None	Unclear because no comparison group: Reduction of 21.5% for intervention that combined clinical and provider education components

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Electronic Decision Support plus Patient Education plus Delayed Prescribing plus Audit & Feedback: Insufficient	Observational: 1 (Patient: NR, Provider: 59)	High	Direct	Unknown	Precise	Not detected	None	Unclear because no comparison group: Inappropriate antibiotic use change from before vs after: Adults: +1.6% (95% CI, -5.4 to 8.5) Children: -1.9% (95% CI, -9.0 to 5.3)
Augmentation Interventions								
Electronic decision support + Communication Education: Moderate	RCT: 1 (12 rural communities, Patients: 407,460, Providers: 334)	Medium	Direct	Unknown	Precise	None	None	Improved appropriate prescribing by 27%
Communication training + clinician education: Low	CRCT: 1 (Patient: 552, Practice: 45, Provider: 30)	Medium	Direct	Unknown	Precise	None	None	No benefit. Antibiotics prescribed according to guidelines: 53.8% vs. 53.1%; adjusted OR 1.03 (95% CI 0.30, 3.09)
2. For patients with an acute RTI and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on antibiotic resistance compared with other strategies or standard care?								
Education, Communication, System Level, Point of Care Testing and Multifaceted Interventions								
	NA	NA	NA	NA	NA	NA	NA	No studies evaluated antibiotic resistance

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Clinical Interventions								
Delayed Prescribing (no prescription) vs. Immediate Antibiotics								
Percent of patients at day 12 with S. pneumoniae resistant to antibiotics: Low	RCT: 1 (223)	Medium	Direct	Unknown	Precise	Not detected	None	At day 12, S. pneumoniae multi-drug resistance was significantly greater in the immediate prescribing group: 4-6: 56% vs. 28%; p<0.02, and resistance to penicillin was lower; p<0.04
3. For patients with an acute RTI and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on medical complications (including mortality, hospitalization and adverse effects of receiving or not receiving antibiotics) compared with other strategies or standard care?								
Education Interventions								
Medical complications: Low	RCT: 1 (2,711,848)	Medium	Direct	Consistent	Precise	Not detected	None	No difference in complications between groups
Medical complications: Low	Observational: 1 (819)	Medium	Direct	Consistent	Precise	Not detected	None	No difference in complications between groups
Communication Interventions								
Admission to hospital: Insufficient	RCT: 1 (2,722; 18 events)	Medium	Direct	Unknown	Imprecise	Not detected	None	Hospitalization in communication group was slightly higher compared with usual care (0.5% vs. 0.2%), and lower compared with CRP testing (0.5% vs. 1.0%). Small number of events.
Clinical Interventions								
Delayed Prescribing Strategies								
Delayed vs. Immediate Prescription								
Diarrhea: (RTI: AOM) Low	RCT: 2 (550)	Medium	Direct	Consistent	Imprecise	Not detected	None	Reduced: Pooled OR: 0.35 (95% CI, 0.21 to 0.59)
Diarrhea: (RTI: Cold) Low	RCT: 1 (129)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference not found: OR 0.82 (95% CI, 0.33 to 2.02)

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Diarrhea: (RTI: Sore throat) Low	RCT: 1 (394)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference not found: OR 1.23 (95% CI, 0.67 to 2.28)
Hospitalization: Insufficient	RCT: 1 (402)	Medium	Direct	Unknown	Imprecise	Not detected	None	1 patient in no antibiotic group developed pneumonia and was admitted to the hospital (0.7%)
Rash: (RTI: AOM) Low	RCT: 1 (285)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference not found: OR 1.21 (95% CI, 0.41 to 3.58)
Rash: (RTI: Sore throat) Low	RCT: 1 (395)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference not found: OR 0.93 (95% CI, 0.41 to 2.11)
Giving prescriptions with instructions vs. leaving prescriptions for collection vs. post-dating prescriptions vs. requesting recontact								
Complications, diarrhea, rash, abdominal pain and vomiting: All Low	RCT: 1 (433)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference not found; Ranges: for complications = 0% in patient-led to 3.7% in recontact; diarrhea = 7% for recontact to 21% for patient-led; rash = 2% for collection to 9% for patient-led; patient-led had higher rates of abdominal pain than recontact (31% vs. 10%) and higher rates of vomiting than collection (18% vs. 4%)

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
C-Reactive Protein Point of Care Testing								
Admission to hospital: Low	RCT: 7 (8,059; 36 events)	Medium	Direct	Consistent	Imprecise	Not detected	None	Potentially increased risk; In two trials, the risk of hospitalization was nonsignificantly increased in CRP testing groups. No events reported in the remaining 5 studies.
Procalcitonin Point of Care Testing								
Mortality: Adults Low	RCT: 5 SR: 2 (2,820)	Medium	Direct	Consistent	Imprecise	Not detected	None	Mortality not shown to be increased (OR 0.32; 95% CI, 0.01 to 7.98)
Composite safety and efficacy: Adults: Treatment Failure at 30 days Low	RCT: 5 SR: 2 (2,820)	High to Medium	Direct	Consistent	Imprecise	Not detected	None	No difference (OR 0.94; 95% CI, 0.72 to 1.22)
Children: Safety Low	RCT: 1 (337)	Low	Direct	Unknown	Imprecise	Not detected	None	A statistically significant difference in safety was not found (OR 1.21; 95% CI, 0.52 to 2.85)
Antibiotic adverse events: Children Low	RCT: 1 (337)	Low	Direct	Unknown	Imprecise	Not detected	None	Higher rate of adverse events in procalcitonin group (26% vs. 10%; 16% absolute difference; OR 3.03; 95% CI, 1.11 to 9.22)
Hospitalization: Children Low	RCT: 1 (337)	Low	Direct	Unknown	Imprecise	Not detected	None	A statistically significant difference in the rate of hospitalization was not found (62% vs. 53%; OR 1.41; 95% CI, 0.68 to 2.93)
Tympanometry Point of Care Testing								
	NA	NA	NA	NA	NA	NA	NA	No studies evaluated this outcome
Rapid Viral Point of Care Testing								
	NA	NA	NA	NA	NA	NA	NA	No studies evaluated this outcome

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
System Level Interventions								
Electronic Decision Support Systems Medical complications: Low	RCT: 1 (NR)	Medium	Direct	Unknown	Precise	None	Low adoption of intervention tools across studies	Within 30 days there was no difference in the proportion of patients diagnosed with pneumonia at revisit.
Electronic Decision Support Systems Hospitalizations: Low	RCT: 1 (NR)	Medium	Direct	Unknown	Precise	None	Low adoption of intervention tools across studies	No difference in rate of hospitalization within 30 days.
Multifaceted Interventions								
Augmentation Interventions								
	NA	NA	NA	NA	NA	NA	NA	No studies evaluated this outcome
Point of Care Tests Combined with Other Strategies								
Hospitalization for CRP + communication vs. usual care, CRP alone, or communication alone: Low	RCT: 1 (4,264 vs. usual, 2,451 vs. CRP, 2,533 vs. communication)	Medium	Direct	Unknown	Imprecise	Not detected	None	Potentially increased risk vs usual care, but not other comparisons: EPC-calculated, unadjusted OR (95% CI) for combination vs. usual = 4.65 (1.21 to 17.87), vs. CRP = 1.07 (0.49 to 2.33), vs. communication = 2.17 (0.85 to 5.50)
4. For patients with an acute RTI and not clear indication for antibiotic treatment, what is the comparative effect of particular strategies on other clinical outcomes (e.g., health care utilization, patient satisfaction) compared with other strategies or standard care?								
Education Interventions								
Return clinic/ED visits (within 2 weeks): Low	RCT: 2 (2,112 patients)	Medium	Direct	Consistent	Imprecise	Not detected	None	No difference in return visits between groups
Overall clinic/ED visits (11-17 month followup): Moderate	RCT: 1 (877)	Medium	Direct	Consistent	Precise	Not detected	None	No difference in new clinic or ED visits between groups

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Overall clinic/ED visits (11-17 month followup): Moderate	Observational: 1 (2,711,848)	Medium	Direct	Consistent	Precise	Not detected	None	No difference in new clinic or ED visits between groups
Satisfaction: Low	RCT: 2 (2,112)	Medium	Direct	Consistent	Imprecise	Not detected	None	No difference in patient or parent satisfaction between groups
Communication Interventions								
Quality of life: Insufficient	RCT: 1 (149/359)	Medium	Direct	Unknown	Imprecise	Not detected	None	Intervention associated with nonsignificant higher physical QOL score (scale 1-100), mean difference of 0.4 (95% CI, -2.6 to 3.3); and nonsignificant lower mental QOL score (scale 1-100), with mean difference of -1.9 (95% CI, -4.9 to 1.1).
Communication vs. Usual Care								
Return clinic visits/reconsultation: Insufficient	RCT: 3 (561/2,830)	Medium	Direct	Inconsistent	Imprecise	Not detected	None	Two trials found increased risk of reconsultation in the communication groups: RRs (95% CI) of 1.3 (0.7 to 2.3) and 1.33 (0.99 to 1.74). Another trial (patient n = 431) found decreased risk of 0.75 (0.57 to 1.00) within 28 days, and a lower mean number of visits for RTI per patient per year during a mean follow-up of 3.67 years (0.36 vs. 0.57; p=0.09).
Improvement in patient symptoms and/or speed or improvement: Low	RCT: 3 (475/3,482)	Medium	Direct	Inconsistent	Imprecise	Not detected	None	Studies used different outcome measures, with diverse findings. Various interventions associated with: improvement in how patients felt (mean difference = 9%; p=0.08); worsened symptom score (mean difference = 0.06; p=0.357); prolonged resolution of symptoms (HR 0.79; p=0.004); and no difference in mean days off of work (3.37 vs. 3.37).
Patient satisfaction: Insufficient	RCT: 1 (40/431)	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference in proportion of patients at least “very satisfied”. 79% vs. 74%; unadjusted RR (95% CI) of 1.06 (0.95 to 1.18).

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Use of other diagnostic tests: Insufficient	RCT: 1 (40/431)	Medium	Direct	Unknown	Imprecise	Not detected	None	Small number of events. No significant differences in use of various diagnostic testing: chest X-ray (5% vs. 7%); blood testing (1% vs. 0%); other (0% vs. 2%).
Communication vs. CRP Testing								
Return clinic visits/reconsultation: Low	RCT: 1 (unclear/2,119)	Medium	Direct	Unknown	Precise	Not detected	None	No significant difference between groups. Unadjusted RR (95% CI) of 0.86 (0.74 – 1.01).
Improvement in patient symptoms and/or speed or improvement: Low	RCT: 2 (~412/2,550)	Medium	Direct	Unknown	Imprecise	Not detected	None	Two studies used different outcome measures. Minimal difference in days off of work (3.37 vs. 3.35); Higher symptom severity score [1.81 (SD 1.02) vs. 1.70 (SD 1.00)]; or median days to resolution of symptoms (6 vs. 5).
Use of other diagnostic tests: Insufficient	RCT: 1 (40/431)	Medium	Direct	Unknown	Imprecise	Not detected	None	Small number of events. No significant differences in use of various diagnostic testing: chest x-ray (5% vs. 5%); blood testing (1% vs. 1%); other (0% vs. 2%).
Communication vs. Education								
Return clinic visits/reconsultation: Insufficient	RCT: 1 (30/552)	Medium	Direct	Unknown	Imprecise	Not detected	None	No association: RR (95% CI) of 0.97 (0.78 to 1.21).
Improvement in patient symptoms and/or speed or improvement: Insufficient	RCT: 1 (30/552)	Medium	Direct	Unknown	Imprecise	Not detected	None	Nonsignificant reduction in days with restricted activity (-0.40; 95% CI, 1.07 to 0.27); and no difference in being off of work (OR 1.00).
Patient satisfaction: Insufficient	RCT: 1 (30/552)	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference in proportion of patients with a maximum patient satisfaction score. Responses highly skewed. 48% vs. 49%; adjusted OR (95% CI) of 1.00 (0.64 to 1.31).

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Clinical Interventions								
Delayed Prescribing Strategies								
Reconsultation ≤ 1 month in cough, children with sore throat or AOM: Moderate	RCT: 4 (990)	Medium	Direct	Consistent	Precise	Not detected	None	No statistically significant difference; rate difference range: -3% to +4%
Reconsultation ≤ 1 month in adults with sore throat: Low	Observational: 1 (11,950)	Medium	Indirect: each vs. no prescription	Unknown	Precise	Not detected	None	Possibly lower risk of reconsultation for new or nonresolving symptoms as minimal overlap in 95% CI's for comparisons to no antibiotics in most conservative model: Delayed = 0.61 (0.50 to 0.74); Immediate = 0.83 (0.73 to 0.94)
Reconsultation ≤ 5-6 months: Low	RCT: 2 (304)	Medium	Direct	Consistent	Imprecise	Not detected	None	No statistically significant difference; rate difference range: -1% to +9%
Reconsultation ≤1 year: Low	RCT: 1 (402)	Medium	Direct	Unknown	Imprecise	Not detected	None	Lower for delayed vs immediate: Delayed = 22% vs. Immediate = 41% vs. No antibiotics = 22%; p=0.0001 for delayed/no vs. immediate
Symptom improvement in Children with sore throat: Low	RCT: 1 (229)	Medium	Direct	Unknown	Imprecise	Not detected	None	Delayed prescribing associated with significantly higher proportion of patients (p<0.0001) patients with severe symptoms at day 3
Symptom improvement in adults with cough: Low	RCT: 1 (402)	Medium	Indirect	Unknown	Imprecise	Not detected	None	Difference not found between delayed and immediate: Mean difference in days (95% CI) for duration of moderately bad symptoms vs. no antibiotics: Delayed antibiotics = 0.14 (-0.87 to 1.14); immediate = -1.08 (-2.1 to -0.09)
Satisfaction across various conditions: Moderate	RCT: 5 (1334)	Medium	Direct	Consistent	Precise	Not detected	None	Lower satisfaction with delayed: Percent of patients satisfied or very satisfied: OR 0.52 (95% CI, 0.35 to 0.76)

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Different Delayed Prescribing Strategies								
Giving prescriptions with instructions, leaving prescriptions for collection, post-dating prescriptions, or requesting recontact: Low	RCT: 1 (433)	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference in median days of symptoms rated as moderately bad (4 for all) or % with reconsultations within 1 month: 14%, 14%, 10%, 18%: p=0.563) or after 1 month: 37%, 32%, 39%, 39%; p=0.391) % patients very satisfied: 89%, 89%, 80%, 74%; p=0.667
Clinical Prediction Score vs. Delayed Prescribing								
Duration in days of symptoms rated as moderately bad or worse: Low	RCT: 1 (325)	Medium	Indirect	Unknown	Imprecise	Not detected	None	Longer for delayed prescribing: Delayed vs. score: 5 vs. 4; HR 1.30 (95% CI, 1.03 to 1.63)
Return within one month: Low	RCT: 1 (325)	Medium	Indirect	Unknown	Imprecise	Not detected	None	Difference not found: Score vs. delayed: 8% vs. 8%; RR 0.91 (95% CI, 0.47 to 1.72)
Return after one month: Low	RCT: 1 (325)	Medium	Indirect	Unknown	Imprecise	Not detected	None	Difference not found: Score vs. delayed: 12% vs. 15%; RR 0.79 (95% CI, 0.47 to 1.29)
C-Reactive Point of Care Testing								
CRP vs. Usual Care								
Return clinic visits/reconsultation: Moderate	RCT: 3 (445/4,810)	Medium	Direct	Consistent	Precise	Not detected	None	Pooled analysis indicates increased risk of reconsultation within 4 weeks RR 1.64 (95% CI 1.35 to 2.00)
Improvement in patient symptoms and/or speed of improvement: Low	RCT: 4 (480/5,622)	Medium	Direct	Inconsistent	Precise	Not detected	None	Studies used different interventions and outcome measures, mostly finding no differences. No significant difference in patients feeling recovered on day 7 (23% vs. 25%, p=0.73; mean days off of work (3.35 vs. 3.37); symptom severity score (1.79 vs. 1.79); or median days to resolution of symptoms (5 vs. 5). One study found “increased or unchanged morbidity” in CRP group (12% vs. 8%; OR 1.6; 95% CI, 1.0 to 2.6).

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Patient satisfaction: Insufficient	RCT: 1 (33/258)	Medium	Direct	Unknown	Imprecise	Not detected	None	No conclusion can be drawn. Higher % of CRP group at least "very satisfied": 76.3% vs. 63.2%; unadjusted RR (95% CI) of 1.21 (1.02 to 1.43).
Use of other diagnostic tests: Chest X-ray Low	RCT: 2* (58/610)	Medium	Direct	Inconsistent	Imprecise	Undetected	None	1) Study in United States with small number of events and no significant difference: 5% (6/110) vs. 7% (8/120); RR (95% CI) of 0.82 (0.29 to 2.28). 2) Study in Russia with higher CXR use and significant difference: 5%/110) vs. 7% (8/120); RR (95% CI) of 1.40 (1.11 to 1.76).
Use of other diagnostic tests: Other, miscellaneous Insufficient	RCT: 1 (40/431)	Medium	Direct	Unknown	Imprecise	Not detected	None	Small number of events. No significant differences in use of various diagnostic testing: chest x-ray (5% vs. 7%); blood testing (1% vs. 0%); other (2% vs. 2%).
CRP vs. Clinical Management Algorithm								
Return clinic visits/reconsultation: Insufficient	RCT: 1 (NR/131)	Medium	Direct	Unknown	Imprecise	Not detected	None	Nonsignificant higher return visits in CRP group: 40% (95% CI, 28% to 52%) vs. 33% (95% CI, 21% to 45%), p=0.46.
CRP vs. Communication Skills Training								
Return clinic visits/reconsultation: Low	RCT: 1 (~ 372/2,119)	Medium	Direct	Unknown	Precise	Not detected	None	Not significantly different between groups. Unadjusted RR (95% CI) 1.16 (0.74 to 1.40).
Improvement in patient symptoms and/or speed of improvement: Low	RCT: 2 (~412/2,550)	Medium	Direct	Unknown	Imprecise	Not detected	None	Two studies used different outcome measures. Minimal difference in days off of work (3.35 vs. 3.37); Lower symptom severity score [1.70 (SD 1.00) vs. 1.81 (SD 1.02)]; or median days to resolution of symptoms (5 vs. 6).
Use of other diagnostic tests: Insufficient	RCT: 1 (40/431)	Medium	Direct	Unknown	Imprecise	Not detected	None	Small number of events. No significant differences in use of various diagnostic testing: chest x-ray (5% vs. 5%); blood testing (1% vs. 1%); other (2% vs. 0%).

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Procalcitonin Point of Care Testing								
Quality of life or illness burden: Adults Insufficient	RCT: 1 (458)	Low	Indirect	Unknown	Imprecise	Not detected	None	No difference between groups.
Days with limited activity: Adults Low	RCT: 2 (1,008)	Medium	Direct	Consistent	Imprecise	Not detected	None	No difference: 9 days in both groups; p=0.854
Days of work missed: Adults Low	RCT: 1 (458)	Low	Direct	Unknown	Imprecise	Not detected	None	No difference in days missed from work; 4.9 and 4.8
Symptoms at 28 days: Adults Low	RCT: 1 (458)	Low	Direct	Unknown	Imprecise	Not detected	None	No difference in % with symptoms at 28 days; 43% in both groups
Tympanometry Point of Care Testing								
Tympanometry Curves: Children Insufficient	RCT: 1 (398)	Medium	Indirect	Unknown	Imprecise	Not detected	None	No difference in curves (normal bilaterally, some movement bilaterally, and flat curve on either side) between groups prescribed an antibiotic or not; p=0.84, 0.14 and 0.10
System Level Interventions								
Return clinic/ED visits: Moderate	RCT: 3 (NR)	Medium	Direct	Consistent	Precise	None	Low adoption of intervention tools across studies	No differences between groups in return clinic visits or ED visits.
Multifaceted Interventions								
Multicomponent								
Patient and clinician interventions combined: Satisfaction Low	RCT: 1 (Patient: 3,843, Provider: 89)	Medium	Direct	Unknown	Imprecise	None	None	Patient satisfaction (% change, SD): 0 vs. 0: No difference Total satisfaction scores 63% vs. 69%; p=0.15

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Patient and clinician interventions combined: Satisfaction Low	Observational: 1 (Patient: 4,489, Provider: 93)	Low	Direct	Unknown	Precise	None	None	No difference; 63% vs. 69%, p=0.15 and adjusted RR 1.1 (95% CI, 0.81 to 1.3).
Overall: Low								
Multifaceted Patient interventions: Insufficient	RCT: 2 (266)	Medium	Direct	Inconsistent	Imprecise	None	None	One study found the satisfaction score higher when no antibiotic was prescribed but the other found no difference in scores.
Reconsultation clinic visits: Insufficient	RCT: 3 (Patient: 821, Provider: 40)	Medium	Direct	Inconsistent	Imprecise	None	None	Two studies find conflicting results for reconsultation for current episode; 0.17 vs. 0.11 (p=0.02) and 10.6% vs. 13.3% (NS) Rate of consultation for subsequent episode, adjusted IRR 1.27 (95% CI, 0.86 to 1.87), p=0.229
Reconsultation clinic visits: Low	Observational: 1 (Patient: 4,489, Provider: 93)	Low	Direct	Unknown	Precise	None	None	Lower for patients Returning for Care within 30 Days: Acute bronchitis: -0.7 vs. -0.2, p=0.08
Overall: Insufficient								

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Point of Care Tests Combined with Other Strategies								
Internet-based provider communication training + CRP for RTI: Resolution of moderately bad symptoms: Low	RCT: 1 (6,771)	Medium	Direct vs. control; Indirect vs. other groups	Unknown	Precise	Not detected	None	Lower for combination and communication alone, but not for CRP alone: Adjusted HR's Control vs. intervention ranged from 0.77 (95% CI, 0.65 to 0.91) for both to 0.87 (95% CI, 0.74 to 1.03) for CRP alone
Small-group face-to-face provider communication training + CRP for lower RTI: Reconsultation, days off work, diagnostic testing use: Low	RCT: 1 (431)	Medium	Direct	Unknown	Imprecise	Not detected	None	Communication training + CRP similar to each alone: Days off work: Range, 3.35 for CRP alone to 3.39 for combined Average reconsultations: Range, 0.18 for communication alone to 0.40 for CRP alone Chest x-ray: 0.05 to 0.05, Blood: 0.01 to 0.05, Other (spirometry, sputum): 0.00 to 0.02
Duration in days of moderately bad or worse symptoms: RADT + clinical score vs. clinical score alone or delayed prescribing: Low	RCT: 1 (489)	Moderate	Direct	Unknown	Imprecise	Not detected	None	No difference: 4 vs. 4 vs. 5; NSD
Return within 1 month: RADT + clinical score vs. clinical score alone or delayed prescribing: Low	RCT: 1 (489)	Moderate	Direct	Unknown	Imprecise	Not detected	None	No difference: 6% vs. 8% vs. 8%, NSD
Return within 1 month: RADT + clinical score vs. clinical score alone or delayed prescribing: Low	RCT: 1 (489)	Moderate	Direct	Unknown	Imprecise	Not detected	None	No difference: 16% vs. 12% vs. 15%, NSD

Key Question Outcome Strength of Evidence Grade	Study Design: Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
5. For patients with an acute RTI and no clear indication for antibiotic treatment, what is the comparative effect of particular strategies on achieving intended intermediate outcomes, such as improved knowledge regarding the use of antibiotics for acute RTIs (clinicians and/or patients), improved shared decisionmaking regarding the use of antibiotics, and improved clinician skills for appropriate antibiotic use (e.g., communication appropriate for patients' literacy level and/or cultural background)?								
	NA	NA	NA	NA	NA	NA	NA	Strength of evidence was not evaluated for these outcomes, as per our protocol
6. What are the comparative nonclinical adverse effects of strategies for improving the appropriate use of antibiotics for acute RTIs (e.g., increased time burden in clinicians, patients, clinic staff)?								
Education, Communication, Clinical (including Point of Care Testing), and System Level Interventions								
	NA	NA	NA	NA	NA	NA	NA	No studies evaluated nonclinical adverse effects of the strategy
Multifaceted Interventions								
	NA	NA	NA	NA	NA	NA	NA	No studies evaluated nonclinical adverse effects of the strategy
Point of Care Tests Combined with Other Strategies								
CRP testing + communication training for clinicians: Low	1 (NR)	Medium	Direct	Unknown	Imprecise	Not detected	NA	Up to 13 minutes more time requires for combined training

Appendix K. Abbreviations Used in Evidence Tables

Table K1. Abbreviations

Abbreviation	Definition
AAFP	American Academy of Family Physicians
ACP	American College of Physicians
AD	academic detailing
AOM	acute otitis media
ARA	antibiotic resistance awareness
ARI	acute respiratory infection
CDC	Centers for Disease Control
CDS	computer-assisted decision-support
CDSS	clinical decision support system
DHMC	Denver Health Medical Center
CHF	congestive heart failure
CI	confidence interval
CME	Continuing Medical Education
COPD	chronic obstructive pulmonary disease
CPGs	clinical practice guidelines
CPR	clinical prediction rules
CRP	C-reactive protein
CVD	cardiovascular disease
DCS	decisional conflict scale
ED	emergency department
EHR	electronic health record
FCHVs	female community health volunteers
FMG	Family Medicine Group
FP	family physician
GERD	gastro-esophageal reflux disease
GP	general practitioner
HMO	Health Management Organization
HR	hazard ratio
ICC	intra-cluster correlation coefficient
ICD-9	international classification of diseases codes
ICE	information and content exchange module
IDSA	Infectious Diseases Society of America
IMS	Information Management System
IMSS	Mexican Institute of Social Security
INF	Influenza
IQR	inter quartile range
IRR	incidence rate ratio
ITT	intention-to-treat
IVDA	intravenous drug abuse
LR	likelihood-ratio test

Abbreviation	Definition
LRTI	lower respiratory tract infection
MCO	Managed Care Organization
MD	Medical Doctor
MV	Matrix variate logistic (MV-logistic) regression model
N	number randomized or enrolled
NA	not applicable
NR	not reported
NS	not significant
OM	otitis media
OME	otitis media with effusion
OR	odds ratio
OTC	over the counter drug
p	p-value
PDS	printed decision support
PCN	Penicillin
PCP	Primary Care Physician
PcV	Penicillin V
PDA	personal digital assistant
PM	personal mailing
POC	point-of-care
QOL	quality of life
RADT	Rapid Antigen Detection Test
RCT	randomized controlled trial
RI	respiratory infection
RN	Registered Nurse
PA	Physicians Assistant
NP	Nurse Practitioner
RR	relative risk
RTI	respiratory tract infection
RX	Prescription
SNAP	safety-net antibiotic prescription
SD	standard deviation
SDM	shared decisionmaking
SES	socioeconomic status
STG	standard treatment guidelines
THC	Thana Health Complexes
TMP-SMX	Trimethoprim (TMP) Sulfamethoxazole (SMX), treatment
UK	United Kingdom
URTI	upper respiratory tract infection
VA	Veterans Affairs
vs.	versus
WBC	white blood cell
WHO	World Health Organization

Abbreviation	Definition
WIC	walk-in clinic

[a] We also ran the Medline search strategy in Scopus on November 4, 2014 in order to identify relevant studies published in EMBASE