WHO Global Guidelines for the Prevention of Surgical Site Infection

Web Appendix 5

Summary of a systematic review on optimal timing for preoperative surgical antibiotic prophylaxis

1. Introduction

The benefit of the routine use of antimicrobial prophylaxis prior to non-clean and implant surgery has long been recognized. Several experimental and clinical studies demonstrated an effect of the timing of surgical antimicrobial prophylaxis (SAP) on surgical site infections (SSI) *(1, 2)*, but the optimal timing remains to be defined.

Several guidelines issued by professional societies or national authorities, such as the American Society of Health-System Pharmacists (ASHP) *(3)*, the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) *(4)*, the Royal College of Physicians of Ireland *(5)*, or Health Protection Scotland *(6)*, recommend administration within 60 minutes prior to incision. However, these recommendations are not based upon systematic reviews of the literature and meta-analysis or a rigorous evaluation of the quality of available evidence.

2. PICO question

How does the timing of SAP administration impact on the risk of SSI and what is the precise optimal timing?

- Population: patients of any age undergoing surgical procedures who need to receive SAP
- Intervention: optimal timing of SAP
- Comparator: reference timing
- Outcome: SSI rates, SSI-attributable mortality

3. Methods

The following databases were searched: Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. The time limit for the review was between 1 January 1990 and 13 August 2014. Language was restricted to English, French, German and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1).

Two independent reviewers screened titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was

obtained. Two authors independently reviewed the full text articles for eligibility based on inclusion criteria. Duplicate studies were excluded.

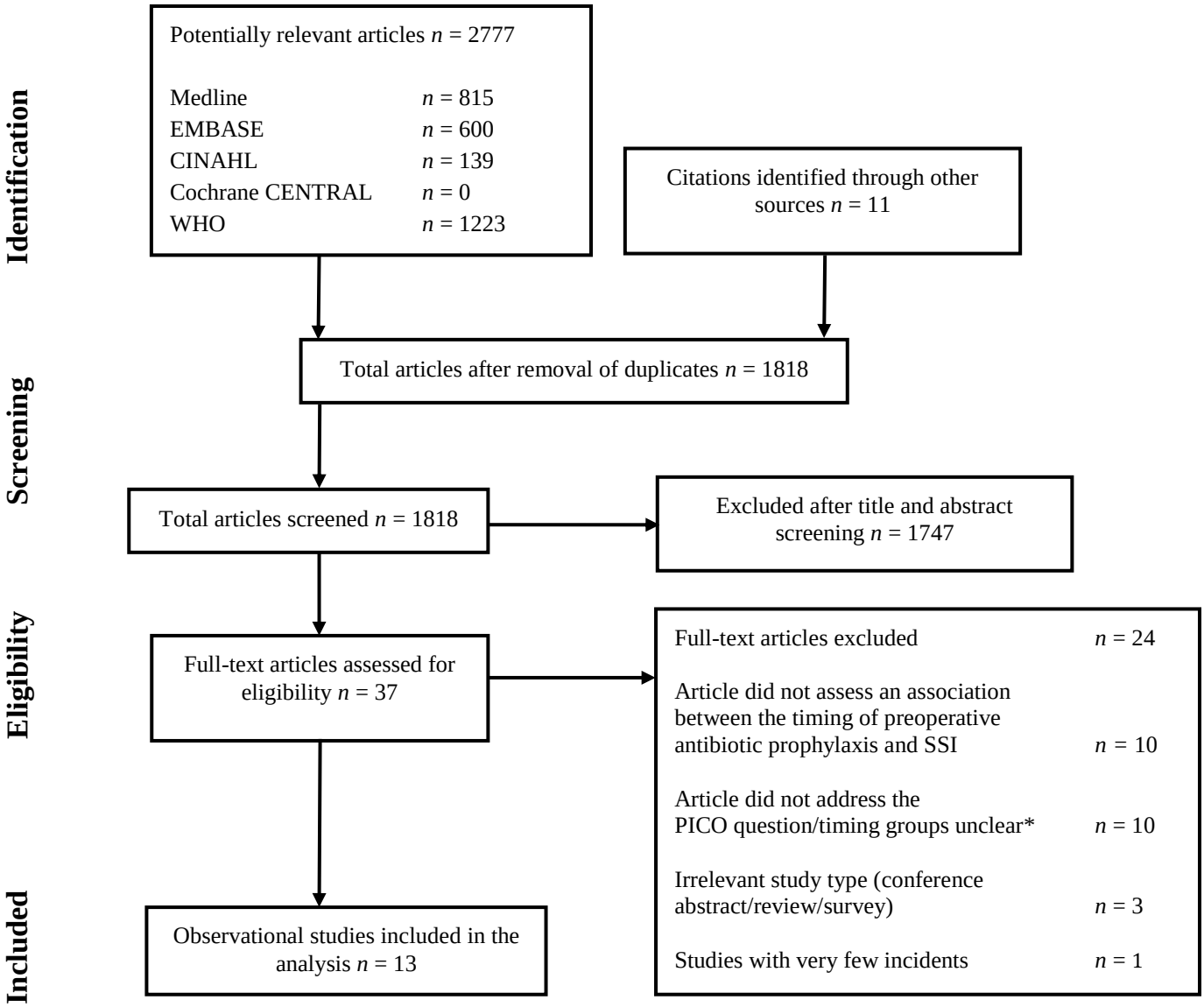
Two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies using the Newcastle-Ottawa Quality Assessment Scale for cohort studies *(7)* (Appendix 3). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons according to different SAP timing intervals were performed using Review Manager v5.3 *(8)* as appropriate (Appendix 4). Adjusted odds ratios (OR) and mean difference with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. Among the studies investigating the interval between 60 and 0 minutes prior to incision, none reported adjusted ORs and we were unable to compare adjusted outcomes for this interval. However, considering the substantial interest in this specific timing (that is, within 60 minutes prior to incision), we used unadjusted crude data as a surrogate for comparison 3a as recommended in other guidelines. In the other comparisons, crude data yielded the same results as adjusted data, but with a different effect size (Appendix 5).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software) *(9, 10)* was used to assess the quality of the body of retrieved evidence (Appendix 6).

4. Study selection

Flow chart of the study selection process



* To avoid drug toxicity, vancomycin and fluoroquinolones have to be infused over a prolonged period of time (>60 minutes) compared to other antibiotics. As timing is measured from the moment of administration and a delay to full infusion is anticipated with the above-mentioned antibiotics, we considered it necessary to differentiate these from fast infusion antibiotics (for example, cephalosporins). Studies that did not have this differentiation were excluded due to unclear timing categories.

5. Summary of the findings

Overall, 13 observational studies comparing different timing intervals for SAP with an SSI outcome were identified. All surgical procedures with an indication for SAP were included (that is, clean-contaminated, contaminated and implant surgery). No randomized controlled trials (RCTs) were found related to the topic. The body of retrieved evidence focused on adult patients; no study was available in the paediatric population. The literature search did not identify any studies that reported on SSI-attributable mortality.

There was a substantial heterogeneity among the included studies. The studies described different arbitrary timing intervals varying from 15 to 120 minutes and not all studies reported the same outcome measures. Despite this heterogeneity in reported time intervals, we were able to make the following comparisons:

SAP administration

1. Pre- vs. post-incision
2. Within 120 minutes vs. more than 120 minutes prior to incision
3. Intervals within 120 minutes prior to incision:
    a. between 120 and 60 minutes prior to incision vs. between 60 and 0 minutes prior to incision
    b. between 60 and 30 minutes prior to incision vs. between 30 and 0 minutes prior to incision

The results of the meta-analyses based on these comparisons are shown in Appendix 5.

1. Four[§] studies *(2, 11-13)* comparing the administration of SAP pre- *vs.* post-incision were identified. Three studies *(2, 12, 13)* reported an increased SSI risk when SAP was administered after incision, although none showed a significant effect. The study by Ho and colleagues *(11)* reported almost no difference (Appendix 2).

   Meta-analysis of these 4 studies showed an increased risk of SSI following SAP administration after incision compared to before incision (OR: 1.89; 95% CI: 1.05-3.4), which resulted in 25 more infections (from one more to 65 more) per 1000 treated patients. For this comparison, the quality of the evidence was low (Appendix 6).

2. Three[§] studies *(2, 14, 15)* comparing the administration of SAP within 120 minutes vs. more than 120 minutes prior to incision were identified. All studies showed a significantly higher SSI risk when SAP was administered more than 120 minutes prior to incision (Appendix 2).

   Meta-analysis of these 3 studies showed that administration more than 120 minutes prior to incision increased the risk of SSI (OR: 5.26; 95% CI: 3.29-8.39) and resulted in 250 more infections (from 154 more to 361 more) per 1000 treated patients. Considering the large effect, the quality of evidence was graded as moderate (Appendix 6).

3. Seven studies *(2, 11-13, 16-18)* comparing intervals of SAP administration within 120 minutes were identified.

    a. Six[§] studies *(2, 12, 13, 16-18)* compared SAP administration within 60 to 0 minutes prior to incision with SAP administration within 120 to 60 minutes prior to incision. Five studies favoured SAP administration within 60 to 0 minutes prior to incision, although none of the studies reached significance. One study favoured administration between 120 and 60 minutes prior to incision, but the results were not significantly different from the interval within 60 to 0 minutes (Appendix 2).

    Meta-analysis[*] of these 6 studies showed that the administration of SAP within 60 to 0 minutes prior to incision had no benefit when compared to administration within 120 to 60 minutes prior to incision (OR: 1.22; 95% CI: 0.92-1.61) and resulted in 6 more (from 2 fewer to 16 more) infections per 1000 treated patients. The quality of evidence was very low due to serious imprecision (Appendix 6).

    **Crude unadjusted data were used in the meta-analyses*

    b. Four[§] studies *(11-13, 17)* comparing SAP administration within 60 to 30 minutes prior to incision with SAP administration within 30 to 0 minutes prior to incision were identified. Ho showed a significant benefit when SAP was administered within 30 to 0 minutes prior to incision. The results reported by Steinberg also favoured administration within 30 minutes prior to incision, but did not reach significance. Weber reported a significantly lower risk when prophylaxis was administered within 60 to 30 minutes prior to incision and van Kasteren also favoured administration within the same time frame prior to incision, but the results did not reach significance.

    Meta-analysis of these 4 studies showed that administration within 30 to 0 minutes prior to incision had neither benefit nor harm when compared to administration within 60 to 30 minutes prior to incision (OR: 1.07; 95% CI: 0.53-2.17) and resulted in 3 more (22 fewer to 50 more) infections per 1000 treated patients. The quality of evidence was very low due to serious heterogeneity and very serious imprecision (Appendix 6).

Four[§] studies *(19-22)* could not be included in any comparison. Trick and colleagues *(19)* conducted a case-control study in a single centre and used a different methodology than other observational studies included in the meta-analysis. They included 120 coronary artery bypass grafting procedures and compared SAP administration within 120 minutes vs. more than 120 minutes prior to incision. The results showed a significantly increased risk of SSI with SAP administration more than 120 minutes prior to incision (OR: 5; 95% CI: 1.4-17) (Appendix 2).

The study by El-Mahallawy and colleagues *(22)* and two studies by Koch and colleagues *(20, 21)* could not be included in the meta-analysis because adjusted ORs could not be derived from their results (Appendix 2). El-Mahallawy and colleagues compared the timing of SAP administration within 30 minutes vs. more than 30

minutes prior to incision in 200 surgical procedures and favoured SAP administration more than 30 minutes prior to incision, but the relation was not statistically significant (*P*=0.115) *(22)*.

The first report by Koch and colleagues was a prospective study evaluating 28 250 cardiac surgical procedures involving median sternotomy and investigated different timings of SAP related to SSI rate reduction. Cefuroxime and vancomycin were administered 15 and 30 minutes prior to incision, respectively *(20)*. The second study compared SAP administration within 30 to 0 minutes prior to incision with SAP administration within 60 to 30 minutes prior to incision in 4453 general surgery procedures. SAP administration within 60 to 30 minutes prior to incision had a 30% higher risk compared to administration within 30 to 0 minutes prior to incision (11.7% vs. 9%) *(21)*. This difference was statistically significant (*P*=0.01).

§ Numbers do not add up to 13 because some studies were included in multiple analyses.

In conclusion, the retrieved evidence can be summarized as follows.

1. Overall, low quality evidence shows that the administration of SAP after incision causes significant harm due to an increase of the SSI risk when compared to administration prior to incision.
2. Overall, a moderate quality of evidence shows that SAP administration before 120 minutes prior to incision causes significant harm due to an increase of the SSI risk compared to administration within 120 minutes.
3. It is not possible to establish more precisely the optimal timing within the 120-minute interval. No significant difference was found between the different time intervals within this period, that is, within 120 to 60 minutes prior to incision vs. within 60 to 0 minutes prior to incision or within 60 to 30 minutes prior to incision vs. within 30 to 0 minutes prior to incision.

    a. Overall, a very low quality of evidence shows that administration within 60 minutes prior to incision has neither benefit nor harm related to the reduction of the SSI rate when compared to administration within 60 to 120 minutes prior to incision.
    b. Overall, a very low quality of evidence shows that administration within 30 minutes prior to incision has neither benefit nor harm related to the reduction of the SSI rate when compared to administration within 60 to 30 minutes prior to incision.

Several limitations can be observed among the available studies. All reported studies are observational. No randomized prospective studies have been done on this topic. Several aspects of the antibiotic regimen differed between studies or were unclear: (a) all studies used multiple agents with varying half-lives; (b) all studies reported the time of administration, but information on infusion time was lacking in many; (c) the duration of the procedure and redosing protocol varied; when a redosing protocol was applied, it was based on the duration of the procedure rather than on the time after the first dose, thus leading to a high risk of inadequate redosing; and (d) postoperative antibiotic duration was not the same. All these aspects influence the effect of timing and also SSI rates.

6. Future research priorities

The systematic review team identified the following key uncertainties and future research priorities.
Future research should focus on an optimal interval within 120 minutes, preferably through randomized prospective trials. The above-mentioned methodological aspects should be well described and standardized in future studies.

APPENDICES

Appendix 1: Search terms

Medline

1. "antibiotic prophylaxis"[MeSH] OR antibiotic prophylaxis [tiab] OR antimicrobial agent*[tiab] OR antimicrobial [tiab] OR antibiotic therapy [tiab] OR antibiotic*[tiab]
2. "surgical wound Infection"[MeSH] OR surgical site infection*[tiab] OR SSI [tiab] OR SSIs [tiab] OR surgical wound infection*[tiab] OR surgical infection*[tiab] OR post-operative wound infection*[tiab] OR postoperative wound infection*[tiab]
3. "time factors"[MeSH] OR timing [tiab]

EMBASE

1. surgical infection/ or (surgical site infection* or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection*).ti,ab,kw.
2. exp prophylaxis/ or exp antibiotic prophylaxis/ or exp antibiotic agent/ or antibiotic*.mp. or antiinfective agent/ct, ad, iv, su
3. exp time/or timing.ti,ab,kw.

CINAHL

1. (MH "surgical wound infection") OR (TI (surgical site infection* OR SSI OR SSIs OR surgical wound infection* OR surgical infection* OR post-operative wound infection* OR postoperative wound infection*) OR AB (surgical site infection* OR SSI OR SSIs OR surgical wound infection* OR surgical infection* OR post-operative wound infection* OR postoperative wound infection*))
2. (MH "antibiotic prophylaxis") OR TI (antimicrobial OR antibiotic*) OR AB (antimicrobial OR antibiotic*)
3. (MH "time factors") OR TI (timing) OR AB (timing)

Cochrane CENTRAL

1. wound infection:ti,ab,kw OR surgical wound infection:ti,ab,kw
2. time:ti,ab,kw OR timing:ti,ab,kw
3. prophylaxis:ti,ab,kw
4. antibiotic:ti,ab,kw

WHO global regional medical databases

1. (SSI)
2. (surgical site infection)
3. (surgical site infections)
4. (wound infection)
5. (wound infections)
6. (postoperative wound infection)
7. (prophylaxis)(prophylactic)
8. (antibiotic)

9. (antimicrobial)
10. (anti infective)
11. (time)
12. (timing)

ti: title; ab: abstract; kw: keyword

Appendix 2. Evidence table

Author, year, reference	Design	Scope	Partici-pants	Type of surgery	SSI definition	Antibiotic used	Duration and re-dosing	Antibiotic continua-tion	Timing categories	Results	SSI rate (%)	Adjusted odds ratio (95% CI)	Risk of bias NOS	Included in compari-son
Classen 1992 ***(2)***	OBS-P	Single centre	2847	Hysterecto my, cholecystec-tomy, bowel resection, gastric bypass, hip, knee.	NA	Cefazolin; cefonicid; cefoxitin; cefamandole	NA	24-48 hours	-24-2 hours - 2-0 hours +0-3 hours +3-24 hours	14/369 10/1708 4/282 16/488	3.8 0.6 1.4 3.3	4.3 (1.8-10.4) 1 2.1 (0.6-7.4) 5.8 (2.4-13.8)	7	1,2,3a
Munoz 1995 ***(15)***	OBS-P	Single centre	2083	Clean-contaminate d, contaminate d and clean.	CDC	Cefazolin; clindamycin + gentamicin; gentamicin + metronidazole ; ceftriaxone; ceftizoxime; cefotaxime; cefoxitin + gentamicin, cefoxitin.	NA	NA	- >2 hours - <2 hours +:	24/107 28/754 94/1222	22.4 3.7 7.7	5.82 (3.12-10.84) 1 3.32 (2.04-5.1)	7	2
Lizán-García 1997 ***(14)***	OBS-P	Single centre	1983	Clean, clean-contaminate d, contaminate d, dirty..	CDC	According to the hospital clinical infections commission	109-146 min; no informatio n on redosing	NA	- >2 hours - <2 hours	5/8 249/197 5	62,5 12.6	5.28 (1.56-17.93) 1	7	2

Trick 2000 ***(19)***	CCTRL	Single centre	120	CABG	CDC DSSI	Cefuroxime	244-252 min; no information on redosing.	NA	- >2 hours - <2 hours			5 (1.4-17) 1	7	
Garey 2006 ***(18)***	OBS-P	Single centre	2048	CABG +valve replacement	CDC	Vancomycin	NA	24 hours	->180 min -121-180 min -61-120 min -16-60 min -0-15 min	21/629 48/700 68/888 6/176 4/15	7.8 6.9 7.7 3.4 26.7	2.1 (0.82-5.62) 2.6 (1.1-6.2) 2.3 (0.98-5.61) 1 11.6 (2.6-24.7)	7	3a
Kasatbipal 2006 ***(16)***	OBS-P	Multi-centre	1972	Open uncomplicated appendectomy	CDC	Metronidazole + gentamicin	<1 hour	24 hours	->1hour: -<1h - intra + None	8/1004 9/814 4/154 5/167	0.7 1.2 2.6 3	0.22 (0.07-0.70) 0.33 (0.11-1.02) 0.78 (0.20-3) 1	7	3
van Kasteren 2007 ***(13)***	OBS-P	Multi-centre	1922	Hip and knee arthroplasty	CDC	Flucloxacillin; erythromycin; clindamycin; cefamandole; amoxicillin; gentamicin	77 min	Yes	->60 min -31-60 min -1-30 min +	5/115 14/538 25/1143 6/126	4.4 2.6 2.2 4.8	1.3 (0.4-4.4) 0.9 (0.4-2.1) 1 2.8 (0.9-8.6)	7	1,3a,3b
Weber 2008 ***(17)***	OBS-P	Single centre	3836	Visceral, vascular, trauma	CDC	Cefuroxim + metronidazole	No information on duration or redosing	Yes	-75-120 min -60-74 min -45-59 min -30-44	15/201 9/263 12/496 33/991 72/1054 39/831	7.5 3.4 2.4 3.3 6.8 4.7	3.16 (1.4-7.0) 1 1 1 2.82 (1.5-5.3)	8	3a,3b

									min -15-29 min -0-14 min			1.75 (0.9-3.4)		
Steinberg 2009 ***(12)***	OBS-P	Single centre	3656	Cardiac, hysterectomy, hip and knee, arthroplasty	CDC	Cephalo-sporins and other short infusion time antibiotics	Re-dosing >4 hours	12-24 hours	- >120 min - 61-120 min - 31-60 min - 0-30 min + 1-30 min + >31 min	4/96 12/489 38/1558 22/1339 4/100 5/74	4.1 2.5 2.4 1.6 4 6.8	2.11 (0.68-6.59) 1.25 (0.57-2.76) 1.74 (0.98-3.08) 1 1.96 (0.65-5.95) 4.18 (1.37-12.75)	8	1,3a,3b
Ho 2011 ***(11)***	OBS-R	Single centre	605	Colon and rectal surgery with anastomosis	CDC	Cefazolin + metronidazole ; cefoxitin; fluoro-quinolone + metronidazole	Re-dosing, duration 3.67 min	24 hours	- >30 min - <30 min +			1.72 (1.15-2.6) 1 0.89 (0.35-2.31)	7	1,3b
Koch 2012 ***(20)***	OBS-P	Single centre	28250	Cardiac surgical procedures involving median sternotomy	STS	Cefuroxime; vancomycin	NA	36 hours	-75 -60 -45 -30 -15 0 +15		- 3.7/ 4.6* - 2.8/ 3.2* - 2.2/ 2.2* -1.9/ 1.8* -1.8 / 2.1* - 2.0 / 2.6* - 2.4 /		6	

											3.3*			
El-Mahallawy 2013 ***(22)***	OBS-P	Single centre	200	Cystectomy, gastrostomy, colorectal surgery	CDC	Penicillin +gentamicin; clindamycin + amikacin	Redose >2 hours; duration 3-4 hours	NA	- > 30 min - < 30 min	12/92 7/108	15 6.9		5	
Koch 2013 ***(21)***	OBS-P	Single centre	4453	General surgery	NSQIP	Cefazolin; ampicillin; ceftizoxime; metronidazole ; ciprofloxacin	Duration< 4 hours; no redosing	NA	- 0-30 min - 30-60 min	284/3140 129/1099	9 11,7		8	

SSI: surgical site infection; -[time]: prior to incision; +[time] : after incision; + : after surgery; NOS = Newcastle-Ottawa Scale, OBS-P: prospective observational cohort; OBS-R: retrospective observational cohort; CCTRL: case-control study; CDC: Centers for Disease Control and Prevention; CABG: coronary artery bypass graft; CI: confidence interval; DSSI: deep sternal site infection; STS: Society of Thoracic Surgeons; NA: not available; NSQIP: national surgical quality improvement programme; *: second value within this cell represents the vancomycin timing group.

Appendix 3. Newcastle-Ottawa risk of bias table

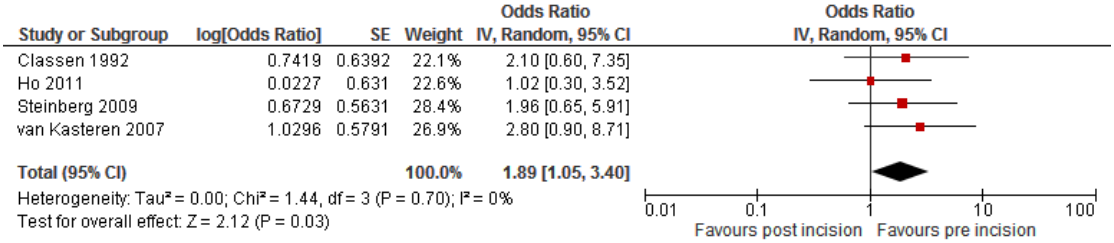
Observational cohort studies **Author, year , reference**	**Representativeness of cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start**	**Comparability of cohorts**	**Assessment of outcome**	**Follow-up long enough**	**Adequacy of follow-up of cohorts**	**Total**
Classen 1992 ***(2)***	B*	A*	A*	Yes*	*	B*	Discharge	A*	7
Munoz 1995 ***(15)***	B*	A*	A*	Yes*	*	A*	Discharge	B*	7
Lizán-García 1997 ***(14)***	B*	A*	A*	Yes*	*	A*	Discharge	A*	7
Garey 2006 ***(18)***	C	A*	A*	Yes*	*	A*	30 days*	A*	7
Kasatpibal 2006 ***(16)***	C	A*	A*	Yes*	*	A*	30 days*	B*	7
van Kasteren 2007 ***(13)***	C	A*	A*	Yes*	*	A*	30 days/1 year*	A*	7
Weber 2008 ***(17)***	B*	A*	A*	Yes*	*	A*	30 days/1 year*	B*	8
Steinberg 2009 ***(12)***	A*	A*	A*	Yes*	*	A*	30 days-1 year*	A*	8
Ho 2011 ***(11)***	C	A*	A*	Yes*	*	A*	30 days*	A*	7
Koch 2012 ***(20)***	C	A*	A*	Yes*		B*	Discharge	A*	5
El-Mahallawy ***(22)***	C	A*	A*	Yes*	*	D	Until removal of stitches	A*	5
Koch 2013 ***(21)***	B*	A*	A*	Yes*		A*	30 days*	B*	7

Case control study **Author, year, reference**	**Is the case definition adequate?**	**Represen-tiveness of cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls**	**Ascertainment of exposure**	**Same method of ascertainment of**	**Non-response rate**	**Total**
Trick 2000 ***(19)***	A*	A*	B	A*	**	A*	Yes*	B	7

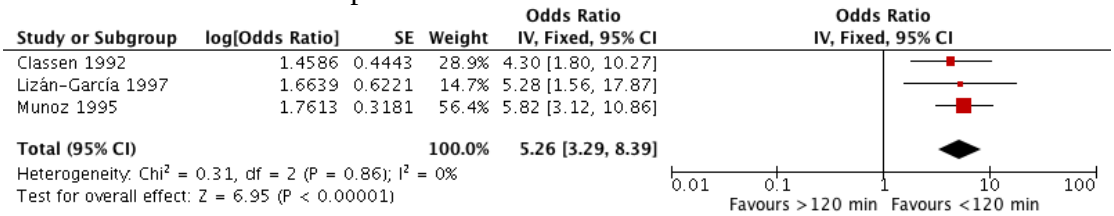
Newcastle Ottawa scale was used. For each * a rating point was added to the total per study

Appendix 4. Meta-analyses using adjusted odds ratios

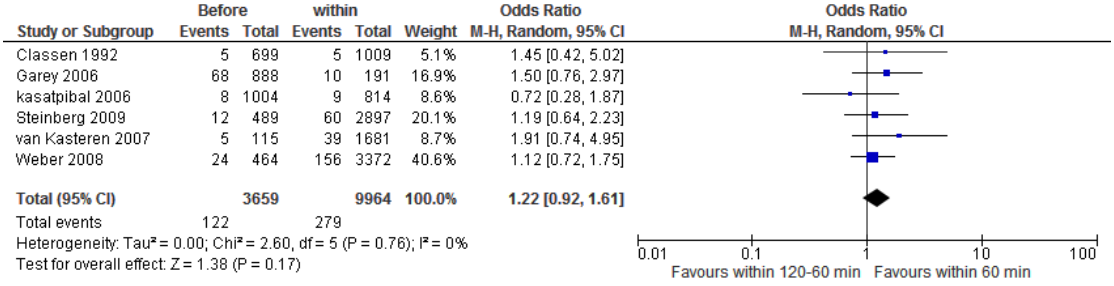
Comparison 1: Administration of surgical antibiotic prophylaxis pre- vs. post-incision



Comparison 2: Administration of surgical antibiotic prophylaxis within 120 minutes vs. more than 120 minutes prior to incision

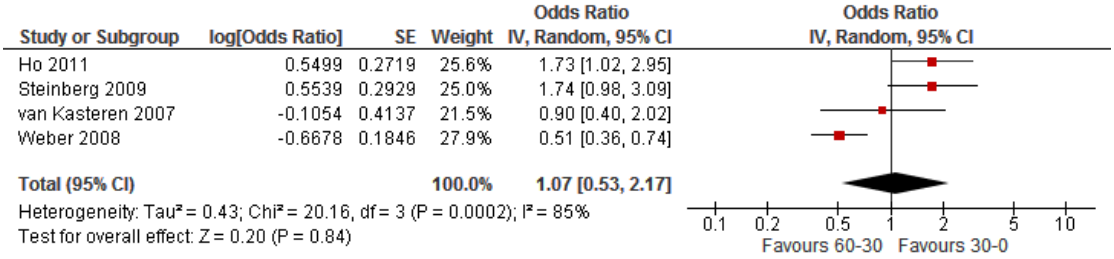


Comparison 3a: Administration of surgical antibiotic prophylaxis within 120-60 minutes vs. within 60 minutes prior to incision.



**Crude unadjusted data were used in the meta-analyses*

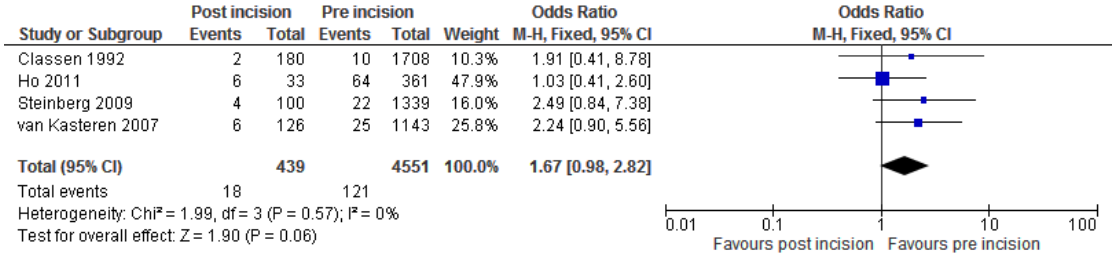
Comparison 3b: Administration of surgical antibiotic prophylaxis 60-30 minutes vs. 30-0 minutes prior to incision.



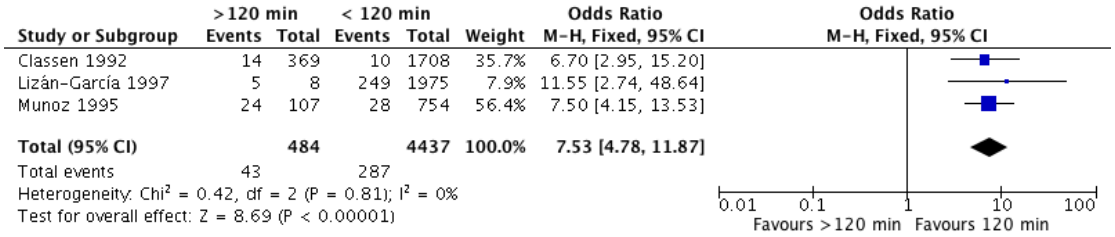
M-H: Mantel-Haenszel (test); CI: confidence interval

Appendix 5. Meta-analyses with crude data

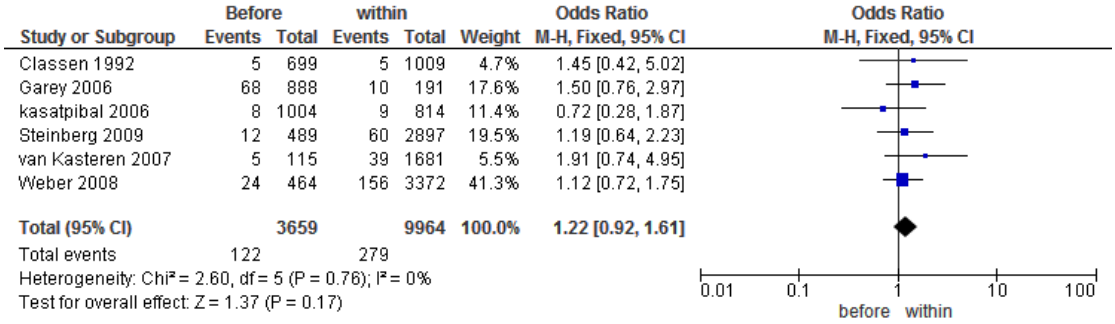
Comparison 1: Administration of surgical antibiotic prophylaxis pre- vs. post-incision.



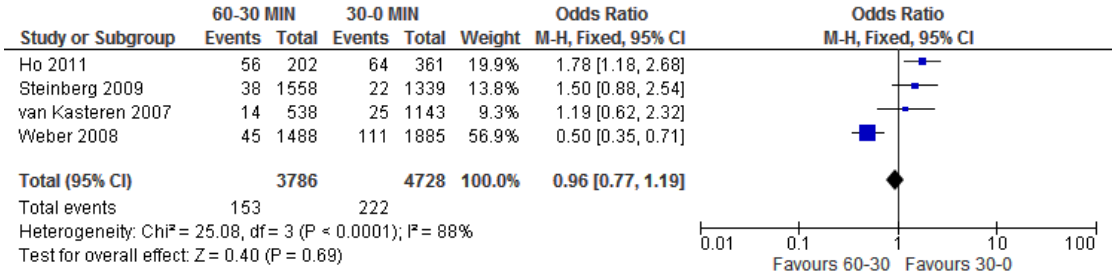
Comparison 2: Administration of surgical antibiotic prophylaxis within 120 minutes vs. before 120 minutes prior to incision.



Comparison 3: Administration of surgical antibiotic prophylaxis within 120-60 minutes vs. within 60 minutes prior to incision.



Comparison 4: Administration of surgical antibiotic prophylaxis within 60-30 minutes vs. 30-0 minutes prior to incision.



M-H: Mantel-Haenszel (test); CI: confidence interval

Appendix 6. GRADE tables

Comparison 1: Administration of surgical antibiotic prophylaxis pre- vs. post-incision

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With SAP administered after first incision**	**With SAP administered before first incision**	**Relative (95% CI)**	**Absolute (95% CI)**	
Surgical site infection											
4	Observational studies	not serious	not serious	not serious	not serious	none	18/439 (4.1%)	116/3852 (3.0%)	**OR: 1.89** (1.05 to 3.40)	**25 more per 1000** (from 1 more to 65 more)	⨁⨁◯◯ LOW

CI: confidence interval; OR: odds ratio; SAP: surgical antibiotic prophylaxis.

Comparison 2: Surgical antibiotic prophylaxis administered within 120 minutes vs. before 120 minutes

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With SAP administered within 120 minutes**	**With SAP administered before 120 minutes**	**Relative (95% CI)**	**Absolute (95% CI)**	
Surgical site infection											
3	Observational studies	not serious	not serious	not serious	not serious	strong association[1]	287/4437 (6.5%)	43/484 (8.9%)	**OR: 5.26** (3.29 to 8.39)	**250 more per 1000** (from 154 more to 361 more)	⊕⊕⊕◯ MODERATE

1. Quality of evidence was upgraded to moderate for large effect size.

CI: confidence interval; OR: odds ratio; SAP: surgical antibiotic prophylaxis.

Comparison 3a: Surgical prophylaxis administered within 120-60 minutes vs. within 60 minutes

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With SAP administered within 120-60 minutes**	**With SAP administered within 60 minutes**	**Relative (95% CI)**	**Absolute (95% CI)**	
Surgical site infection											
6	Observational studies	not serious	not serious	not serious	serious [1]	none	122/3659 (3.3%)	279/9964 (2.8%)	**OR: 1.22** (0.92 to 1.61)	**6 more per 1.000** (from 2 fewer to 16 more)	⨁◯◯◯ VERY LOW

*Crude unadjusted data were used in the meta-analyses

1. Optimal information size is met but the CI overlaps no effect and fails to exclude considerable benefit or harm (RR or RRR of 25%)

CI: confidence interval; SAP: surgical antibiotic prophylaxis; OR: odds ratio; RR: relative risk; RRR: relative risk reduction.

Comparison 3b: Surgical antibiotic prophylaxis administered within 60-30 minutes vs. within 30-0 minutes

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With SAP administered within 60-30 minutes**	**With SAP administered within 30-0 minutes**	**Relative (95% CI)**	**Absolute (95% CI)**	
Surgical site infection											
4	Observational studies	not serious	serious[1]	not serious	serious[2]	none	153/3785 (4.0%)	222/4728 (4.7%)	**OR: 1.07** (0.53 to 2.17)	**3 more per 1000** (from 22 fewer to 50 more)	⊕◯◯◯ VERY LOW

1. High heterogeneity, $I^2 = 85\%$
2. Optimal information size is met but the CI overlaps no effect and fails to exclude considerable benefit or harm (RR or RRR of 25%)

CI: confidence interval; SAP: surgical antibiotic prophylaxis; OR: odds ratio; RR: relative risk; RRR: relative risk reduction.

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