



World Health
Organization

**GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC
SEXUALLY TRANSMITTED INFECTIONS**



**WEB ANNEX G. SYSTEMATIC REVIEW
ON THE ROLE OF *MYCOPLASMA
GENITALIUM* IN ACUTE AND PERSISTENT
URETHRAL DISCHARGE AND PELVIC
INFLAMMATORY DISEASE**

JUNE 2021

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Guidelines for the management of symptomatic sexually transmitted infections: Web Annex G. Systematic review on the role of *Mycoplasma genitalium* in acute and persistent urethral discharge and pelvic inflammatory disease

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Introduction

Mycoplasmas, the trivial name for members of the class Mollicutes, are the smallest free-living microorganisms. They lack the rigid cell wall of other bacteria and, consequently, resist penicillins and other β -lactam antibiotics.

In the urogenital tract, the relevant Mollicutes are *M. genitalium*, *M. hominis* and the ureaplasmas. The present review will address only the evidence base for the role of *M. genitalium* in male urethritis and in pelvic inflammatory disease (PID).

Methodology

A literature search in PubMed and Biosis was conducted in June 2018 using the search term "genitalium". Abstracts from conferences in infectious diseases, microbiology, and sexually transmitted infections were retrieved from the Biosis search and manually searched in online and paper-based abstract books from conferences within the recent five years in order to identify research not yet published in peer-reviewed literature.

All abstracts were scanned for relevance and full papers of possible interest were retrieved and analysed. After each article was read, a determination was made as to whether it provided data relevant to the scope of the review.

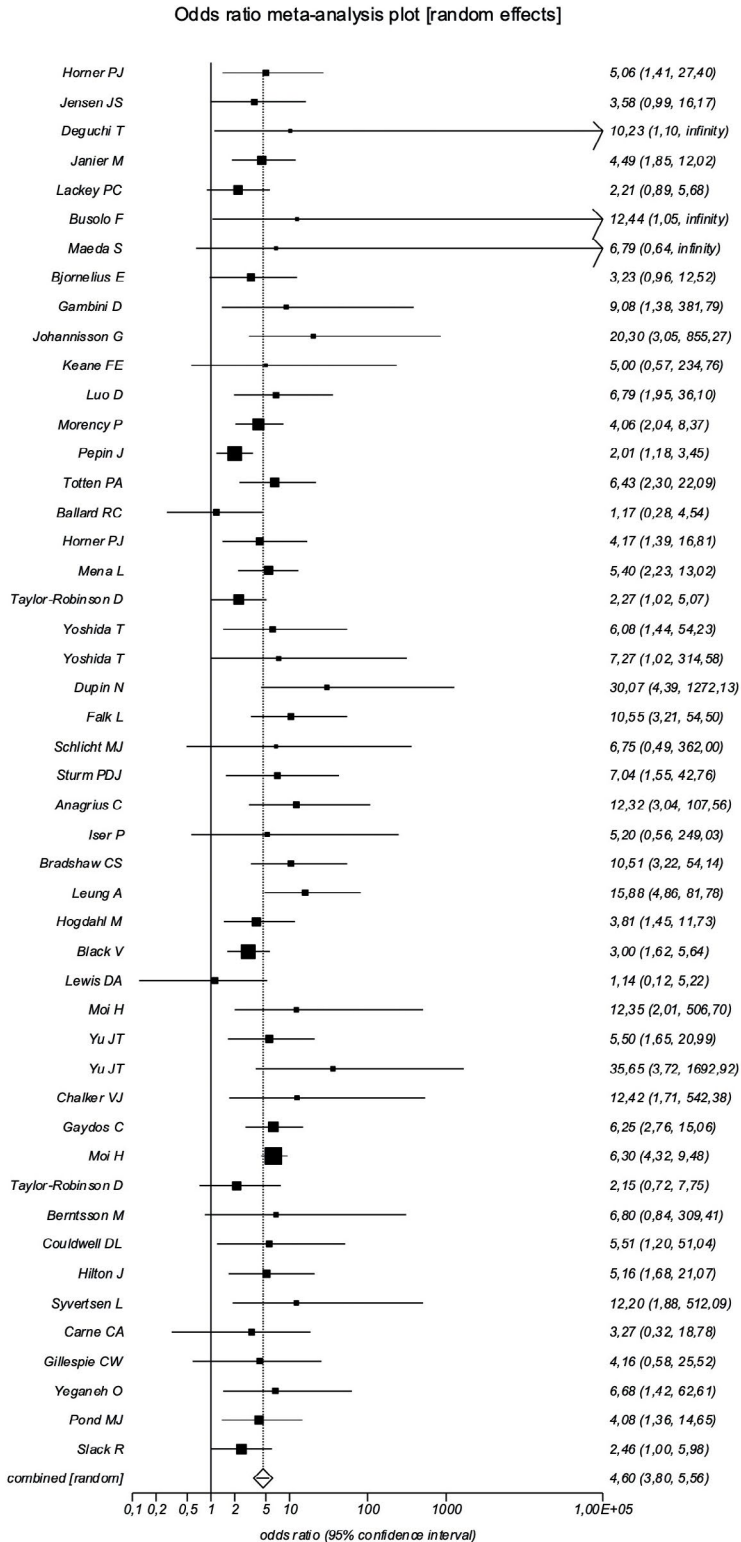
Tables of evidence containing journal reference, abstract, extracted data as well as a subjective evaluation of the quality of the paper were created as an excel file with each outcome on a separate datasheet.

A repeat literature search was conducted by the end of September 2018 in order to retrieve the most recent additions to the literature.

Male urethritis

Acute non-gonococcal urethritis

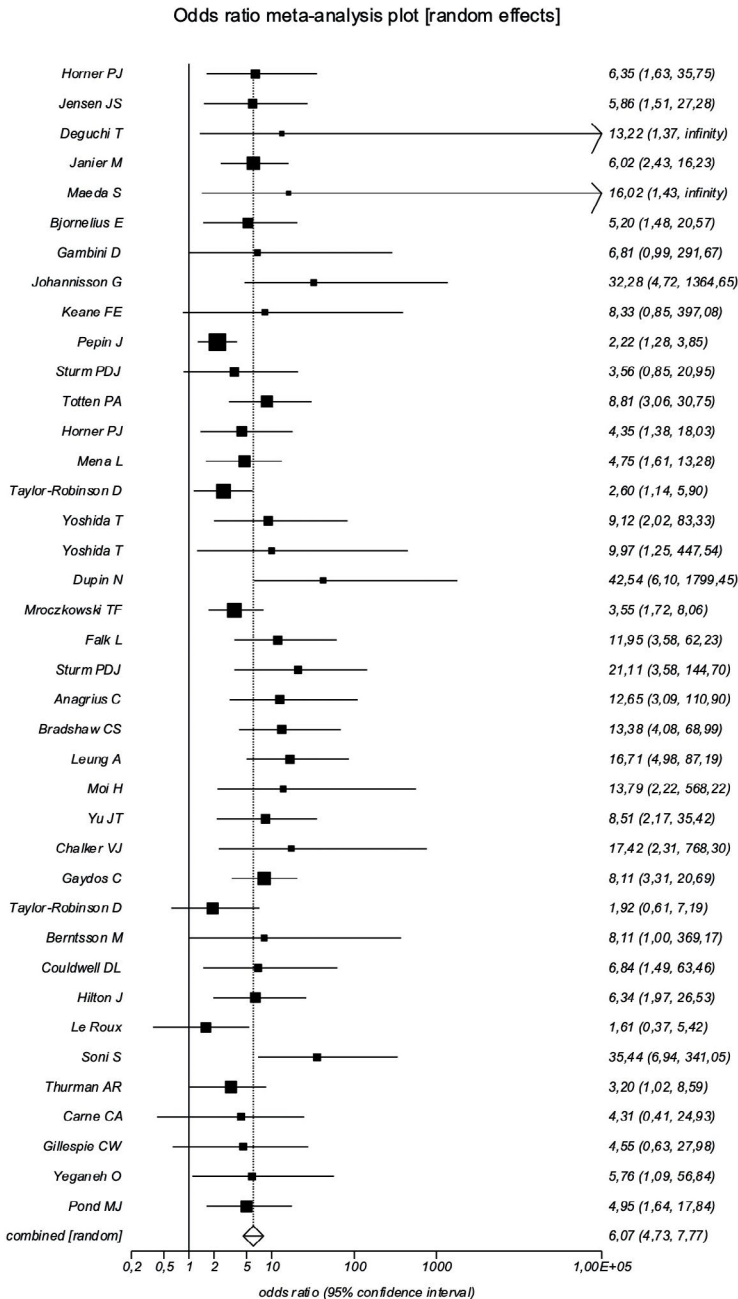
M. genitalium was strongly associated with male acute non-gonococcal urethritis (NGU). It has been detected by use of nucleic acid amplification tests (NAATs) in 48 studies of acute NGU where controls without urethritis were included, and has been detected in this group with a median of 14% (range 3 – 42%) of cases compared with a median of 2.5% (range 0 – 18%) in controls. Analysing the 48 dataset for odds-ratios using random effects (DerSimonian-Laird), a pooled odds ratio of 4.6 (95% CI = 3.8 to 5.6) was found. A Forrest plot illustrating the odds-ratios for the individual studies is shown in figure 1.

Figure 1. Odds-ratios for studies of *M. genitalium* associated NGU and controls

Acute non-chlamydial-non-gonococcal urethritis (NCNGU)

A total of 39 papers contained data on non-chlamydial NGU (NCNGU) with controls, and the association was even stronger with *M. genitalium* being detected in a median of 20% (range 4 - 45%) of cases. Analysing the 39 dataset for odds-ratios using random effects (DerSimonian-Laird), a pooled odds ratio of 6.1 (95% CI = 4.7 to 7.8) was found. A Forrest plot illustrating the odds-ratios for the individual studies is shown in figure 2.

Figure 2. Odds-ratios for studies of *M. genitalium* associated NCNGU and controls



Persistent or recurrent urethritis

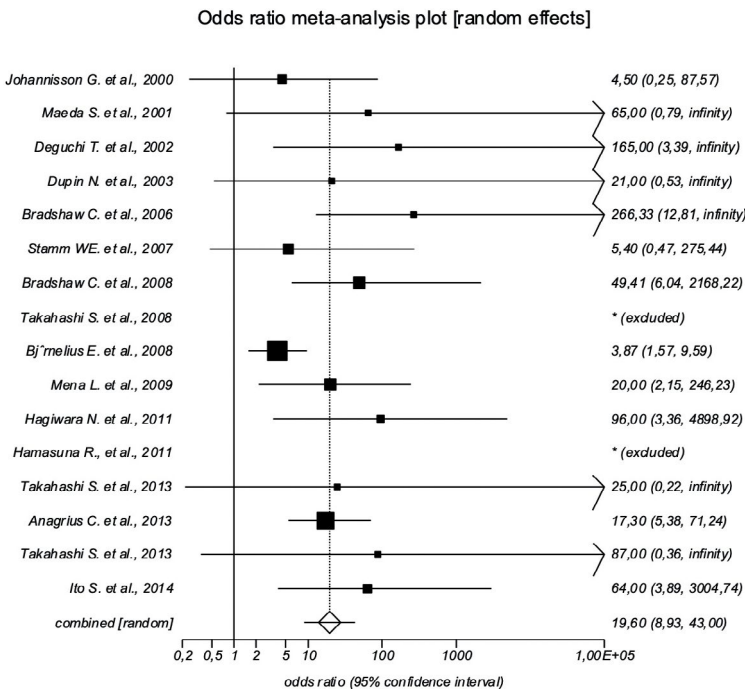
Due to the poor efficacy of standard NGU treatment, *M. genitalium* is strongly associated with recurrent or persistent NGU being detected in up to 41% of men failing doxycycline therapy (Wikström & Jensen, 2006).

A total of five studies have been published addressing men with persistent or recurrent urethritis with one study including men with post-gonococcal urethritis where the majority of the patients had urethritis caused by *C. trachomatis* (Yokoi *et al.*, 2007). In the four studies of persisting or recurrent NGU, the proportion of urethritis caused by *M. genitalium* ranged from 15 to 41% with an overall prevalence of 27% among 230 patients studied.

Twenty studies addressed the effect of treatment of *M. genitalium* positive urethritis and 19 contained data on the presence of urethritis in patients where antibiotic treatment failed to eradicate the infection. Of the 248 patients with persistent *M. genitalium* infection, 230 (93%) had urethritis. In the 16 studies including data on both men with persistent and eradicated *M. genitalium* infection, 222 patients had persistent *M. genitalium* infection and 180 (85%) had urethritis compared to the 350 patients where *M. genitalium* was successfully eradicated among whom only 77 (22%) had urethritis ($p > 0.0001$).

Analysing the 16 dataset for odds-ratios using random effects (DerSimonian-Laird), a pooled odds ratio of 19.6 (95% CI = 8.9 to 43.0) was found. A Forrest plot illustrating the odds-ratios for the individual studies is shown in figure 3. Two studies reported no treatment-failures and ORs could therefore not be calculated (Takahashi *et al.*, 2008) (Hamasuna *et al.*, 2011).

Figure 3. Odds-ratios for persistent or recurrent urethritis in patients with and without eradication of *M. genitalium*



Pelvic inflammatory disease (PID)

There is accumulating evidence that *M. genitalium* is a cause of PID. However, the clinical PID diagnosis is notoriously difficult (Sellors *et al.*, 1991), and laparoscopy is rarely performed. Furthermore, laparoscopy will primarily detect salpingitis and will often fail to identify even severe endometritis. Endometritis has been diagnosed in a number of studies by microscopy of endometrial biopsies. The diagnostic accuracy of this approach, however, has also been questioned, as plasma cell endometritis can be found also in apparently healthy women (Vicetti Miguel *et al.*, 2011).

In lower monkeys, *M. genitalium* caused acute salpingitis and parametritis with an antibody response when it was introduced into the oviducts (Moller *et al.*, 1985), and in Fallopian-tube organ cultures, in which the tissues are maintained in a condition similar to that *in vivo*, *M. genitalium* causes damage with swelling and necrosis of the epithelium (Baczynska *et al.*, 2007).

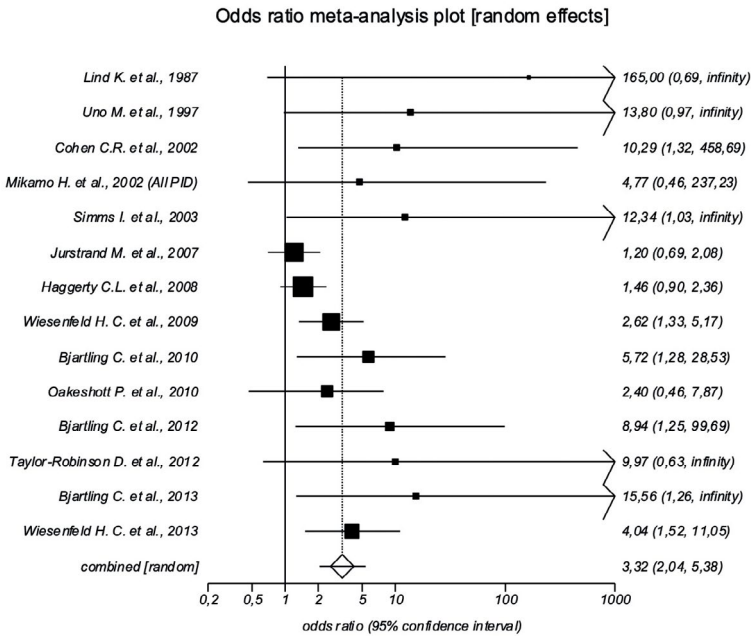
A total of 24 publications addressing *M. genitalium* and PID were identified during the literature search. One congress abstract could not be retrieved and was excluded. Five studies were based on the PEACH (PID Evaluation And Clinical Health) study population, and for the meta-analysis, only the study addressing the association between histological endometritis and *M. genitalium* was included (Haggerty *et al.*, 2008). One study appeared twice (Simms *et al.*, 2003b; Simms *et al.*, 2003a) in the search as it was co-published in two journals. Only one of the versions was included in the analysis.

Three studies were based on serology with different methodologies. One did not include a control group (Moller *et al.*, 1984), but suggested that 40% of non-chlamydial, non-gonococcal, non-*M. hominis* PID could be explained by *M. genitalium* infection. A second study (Lind & Kristensen, 1987) did not show an association although *M. genitalium* was found in 1 of 21 (5%) of cases and in none of the 7 controls. In the third study (Jurstrand *et al.*, 2007) no association between *M. genitalium* antibodies and PID could be demonstrated when the complete dataset was analysed. However, a sub-analysis of women between 15 and 30 years of age showed an OR of 1.9 for PID although this was not statistically significant. Interestingly, the presence of chlamydial antibodies in women >30 years also lacked statistical association with PID. Considering the age-spectrum of *M. genitalium* and *C. trachomatis* infections, these observations make sense, as serology primarily indicates previous exposure. An additional fourth study (Taylor-Robinson *et al.*, 2012) used supplementary serological investigations to define infection. Due to the heterogeneity of the serological studies these are not analysed separately but those that contained controls are included in the complete analysis.

Two studies (Cohen *et al.*, 2005; Savaris *et al.*, 2007) determined the prevalence of *M. genitalium* in women with PID, but did not include a control group. They found a prevalence of 7% and 5%, respectively.

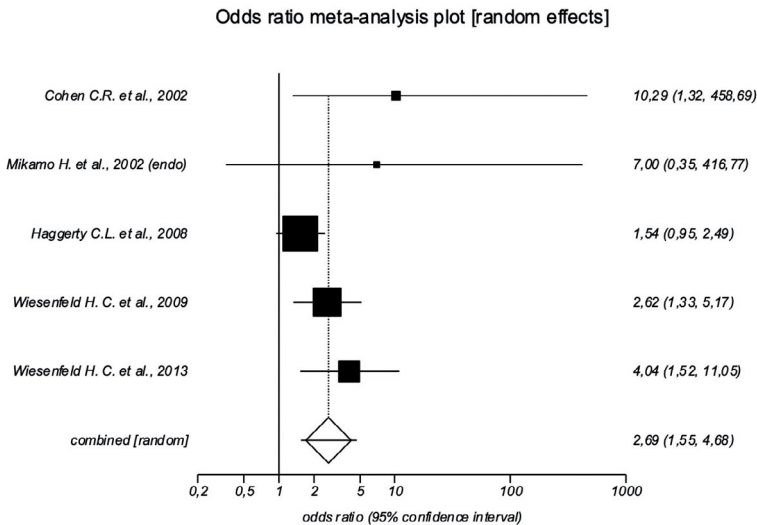
In the complete analysis, 14 studies comprising control populations, including two based only on serology (Lind & Kristensen, 1987; Jurstrand *et al.*, 2007) and one with combined serology and PCR (Taylor-Robinson *et al.*, 2012), all studies had odds-ratios larger than 1, although many of the studies were small and had large confidence intervals. Using random effects (DerSimonian-Laird), a pooled odds ratio of 3.32 (95% CI = 2 to 5.4) was found. A Forrest plot illustrating the odds-ratios for the individual studies is shown in figure 4. Using all 16 studies with data on the prevalence of *M. genitalium* in PID cases, *M. genitalium* was detected in 192 of 1441 PID cases (13%)

Figure 4. Odds-ratios for PID in women with *M. genitalium* infection detected by PCR either in the lower or the upper genital tract and/or serology



A subset of 5 studies used the uniform criterion of histological endometritis. The combined odds-ratio was 2.7 (95% CI = 1.6 to 4.7). A Forrest plot illustrating the odds-ratios for the individual studies is shown in figure 5.

Figure 5. Odds-ratios for endometritis in women with *M. genitalium* infection detected by PCR either in the lower or the upper genital tract



Conclusion

Examination of specimens for *M. genitalium* by PCR has established that it is a cause of non-gonococcal urethritis and non-chlamydial-NGU causing at least 15% of NGU and 20% of NCGU. In chronic/persistent NGU, *M. genitalium* is a cause in more than 25%, and 85% of patients with persistent *M. genitalium* infection after antibiotic treatment failure have urethritis. Thus, *M. genitalium* is an important cause of male urethritis.

In pelvic inflammatory disease the presence of *M. genitalium* in the cervix and/or upper genital tract is associated significantly with histological endometritis. Furthermore, it has been detected in the tubes, although rarely. In one study, a significant antibody response to *M. genitalium* was detected in about 30% of women with pelvic inflammatory disease in whom antibody responses to *M. hominis* and *C. trachomatis* could not be detected; in other studies, however, an association of this kind was not demonstrated. Based on the combined evidence, it appears highly likely that *M. genitalium* is a cause of PID and may explain approximately 13% of PID, most having a milder course comparable to that caused by *C. trachomatis*.

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