

Exploring the implications for coincidental treatment of *Mycoplasma genitalium* infection in *Neisseria gonorrhoeae*-positive patients

Lebogang P. Mhango^{1†}, Ella Trembizki ^{1†}, Caroline Thng², David M. Whiley^{1,3} and Emma L. Sweeney^{1*}

¹The University of Queensland Centre for Clinical Research (UQ-CCR), Queensland, Australia; ²Gold Coast Sexual Health & HIV Service, Queensland, Australia; ³Pathology Queensland Central Laboratory, Queensland, Australia

*Corresponding author. E-mail: e.l.sweeney@uq.edu.au

†Lebogang P. Mhango and Ella Trembizki contributed equally to this manuscript.

Sir,
Mycoplasma genitalium is an important sexually transmissible infection (STI), with rates on the rise in both heterosexuals and MSM. Despite increases in the rates of *M. genitalium*, STI guidelines typically do not recommend routine screening for this pathogen unless patients are symptomatic and present with cervicitis or urethritis.¹⁻³ This is due to its clinical significance not being well understood and somewhat controversial.⁴⁻⁸ Moreover, it is prudent to consider the disadvantages of macrolide usage on *M. genitalium* asymptomatic patients and its potential pathway to further antimicrobial resistance, particularly due to suboptimal dosages (i.e. 1 g). Accordingly, in Australia, treatment regimens for confirmed *M. genitalium* involve a 7 day course of 100 mg doxycycline, followed by 4 days of azithromycin (1g immediately and 500 mg daily for 3 days), similar to treatment guidelines from the British Association for Sexual Health and HIV in the UK.^{2,9} Moreover, the CDC has recently released new treatment guidelines for gonococcal infection: a single 500 mg dose of ceftriaxone for uncomplicated infections where chlamydia has been excluded.¹⁰

In recent years, studies in Australia, the UK, Singapore, Spain and the USA have looked at *M. genitalium* coinfection with other STIs to better understand its prevalence. These studies have identified *M. genitalium* coinfection in 4.8% of patients infected with *Neisseria gonorrhoeae* in Spain,¹¹ between 5% and 7.9% in Australia,^{8,12} 1.9% in the USA¹ and 2.4% in Singapore;⁶ further highlighting issues of silent carriage of *M. genitalium* infections that could otherwise be missed and/or go untreated. However, a recent study in Sydney, Australia, suggested there is potential for incidental treatment of *M. genitalium* infections in men administered 1g azithromycin as part of standard-of-care gonorrhoea treatment.¹² In this study, we sought to explore the baseline risk of *N. gonorrhoeae*-positive individuals coinfecting with *M. genitalium* in Queensland, Australia. In doing so, we sought to understand (i) the extent of *N. gonorrhoeae* and *M. genitalium* coinfections in both men and women in Queensland and (ii) the implications for incidental treatment of *M. genitalium* infections with the macrolide azithromycin, noting that dual ceftriaxone/azithromycin therapy

(500 mg IV and 1–2 g oral, respectively) is also used in Queensland for gonorrhoea infection.

A total of 600 *N. gonorrhoeae*-positive clinical samples submitted to Pathology Queensland for routine STI testing in the period January to June 2019 were de-identified and retrospectively screened for *M. genitalium* using the commercially available ResistancePlus[®] MG kit (SpeeDx, Sydney, Australia), which simultaneously detects *M. genitalium* and the five most common 23S rRNA mutations (A2058T, A2058C, A2058G, A2059C and A2059G).

We identified that almost 6% (35/600) *N. gonorrhoeae*-positive patients were also infected with *M. genitalium*. Coinfections were observed in 11.0% (17/155) of females and 4.4% (19/436) of males, with females accounting for almost half (48.6%; 17/35) of all coinfections reported within our study. Nine samples had no gender associated with them.

In 2019, 7.9% (563/7091) of women were positive for *M. genitalium* infections in Queensland (Pathology Queensland notification data). Comparatively, our cohort recorded an 11% rate of *M. genitalium* coinfection in females, of whom the majority (94.8%) were in their reproductive years (<45 years old). Rates of coinfection within our study are in line with previous limited studies, which identified 33% (4/12) *Chlamydia trachomatis*/*N. gonorrhoeae* coinfections with *M. genitalium* in females.¹¹ Studies in the USA, UK and Singapore demonstrated lower rates of coinfection with *N. gonorrhoeae*, between 0% and 2.8% in their female cohorts.^{1,5,6}

Not all patients who were screened for *N. gonorrhoeae* in this study would have also been screened for *M. genitalium*. However, our study demonstrated the possibility of incidentally treating nearly half of *M. genitalium* coinfections through dual therapy of *N. gonorrhoeae*, including up to 52.9% of *M. genitalium* infections in females via standard-of-care *N. gonorrhoeae* treatment. This is an important finding, as similarly to gonorrhoea only half of women with *M. genitalium* infection present with symptoms. Thus there are clear implications for incidental treatment to have a positive effect on eradication of *M. genitalium* and prevention of additional serious complications such as infertility, pelvic inflammatory disease and ectopic pregnancy in reproductive-age women

experiencing these infections.⁷ Conversely, among *M. genitalium*-positive patients, 54.3% (19/35) harboured macrolide resistance mutations, which is similar to macrolide resistance levels reported by Sweeney *et al.*,¹³ and therefore may not be treated with *N. gonorrhoeae* treatment regimens.

There are some limitations of this study. Firstly, we were unfortunately unable to confirm if these patients were otherwise tested or treated for *M. genitalium* infections. Further, we cannot assume all patients received standard *N. gonorrhoeae* treatment, which includes ceftriaxone and azithromycin, and we were also unable to assess if these *M. genitalium* infections were successfully eradicated via coincidental azithromycin treatment. Nevertheless, this study provides evidence that nearly half of *M. genitalium* coinfections in Queensland may be indirectly treated through dual therapy for *N. gonorrhoeae*. Our data do not support the need for expanded screening of *M. genitalium*, despite the possibility of eradicating additional infections through coincidental azithromycin treatment; this approach may not outweigh antimicrobial stewardship when it comes to macrolide use as evidenced by increased resistance in a range of bacteria.

Further, caution is still warranted in interpretation of these results, as the balance of incidental treatment must be weighed with successful treatment and provision of test of cure, appropriate contact tracing/partner treatment and the risk of selection of further macrolide resistance in *M. genitalium*.

Acknowledgements

We wish to thank Pathology Queensland staff for their assistance in providing nucleic acid samples for this study.

Funding

This work was supported by a Queensland Advancing Clinical Research Fellowship from the Queensland Government, held by David M. Whiley. Testing kits were provided in kind by SpeeDx Australia Pty Ltd.

Transparency declarations

David M. Whiley declares funding from SpeeDx Australia. All other authors: none to declare.

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