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M. genitalium on the loose: time to sound the alarm

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Mycoplasma genitalium has been receiving increasing attention over the years, in part due to the recognition that it is strongly associated with male and female reproductive tract disease syndromes [1, 2], and in part due to the increasing spread of antibiotic resistance [3]. The latter is reflected in two studies published in this issue of the journal. Barberá and colleagues provide the first report of the prevalence of antibiotic resistance in Spain [4], a region with relatively little epidemiologic data on *M. genitalium*. Chernesky and colleagues estimated *M. genitalium* prevalence using self-obtained meatal swab sampling and report the prevalence of macrolide resistance among Canadian males attending a healthcare center for street youth [5].

Barberá and colleagues tested stored specimens from 84 Spanish men and women with positive *M. genitalium* tests [4]. Macrolide resistance mediating mutations (MRMM), which are strongly associated with azithromycin treatment failures [3], were identified in 34%. These mutations were nearly 9-fold more likely in individuals that had received treatment with azithromycin in the prior year, and 11.5 times more likely in men that reported sex with other men (MSM). Mutations in the *parC* region of the quinolone resistance determining region (QRDR), the most common mutations associated with moxifloxacin treatment failures [3], were found in 8%. Three people (3.6% of tested specimens) had both macrolide and quinolone resistance-associated mutations, suggestive of dual drug resistance.

Chernesky et al summarized a validation study comparing self-obtained meatal swab specimens to first catch urine for detecting five sexually transmitted pathogens, of which *M. genitalium* was one [5]. Irrespective of the specimen type used, *M. genitalium* was more common than any of the four other STIs (15.3% with meatal swab and 12.6% in urine) and self-sampling using a meatal swab yielded higher prevalence of all five STIs. Although assays to detect mutations in the QRDR were not performed, MRMM were detected in 55.9% of urine specimens with readable 23S rRNA sequences, consistent with an earlier report of 50% in US men and women [6].

Chernesky et al's report is the most recent in a series where the balance of *M. genitalium* and C. trachomatis prevalence of has shifted. In 2001-2002, the prevalence of *M. genitalium* among young adults in the US was 1.0% compared to 4.2% for *C. trachomatis* [7, 8], yet in 2010-2012 *M. genitalium* prevalence in Great Britain's NATSAL-3 was similar to that of *C. trachomatis* (1.2% vs 1.1% in men; 1.3% vs 1.5% in women) [9, 10]. Similarly, in early

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studies of higher risk clinic patients, *M. genitalium* prevalence was lower than *C. trachomatis* in Sweden (6% vs 10%) [11] and the US (7.0% vs. 11.1%) [12], yet in 2016 *M. genitalium* prevalence in seven U.S. clinics was substantially higher than chlamydia in women (16.3% vs. 9%, respectively) and approximately the same in men (17.2% vs. 17.8%) [6]. Rising prevalence may be due to increased detection when more sensitive tests are implemented or increased incidence of infection subsequent to either changes in risk behavior or longer duration of infectiousness. Neither the sensitivity of diagnostic assays nor risk behavior has changed dramatically in recent years. Instead, the data presented by Chernesky and Barbera suggest that antibiotic resistance-related treatment failure, which can extend the duration of infection and infectiousness, may be at play.

Relatively early in our understanding of the epidemiology of *M. genitalium*, it became evident that antibiotic resistance occurred rapidly. Bradshaw and colleagues first reported treatment failures in 28% of Australian men with *M. genitalium* subsequent to therapy with azithromycin in 2006 [13]. Since the initial publication of this finding, the number of studies reporting antibiotic resistance in *M. genitalium* has been increasing in an almost exponential fashion. In the first 5 months of 2017 alone, 8 new reports of resistance in *M. genitalium* appeared in the literature (PubMed Search, May 8, 2017).

In these most recent reports, the prevalence of MRMM ranged from a low of 4.6% in 4 Russian cities [14] to a high of 74% in Auckland, New Zealand [15]. In Melbourne Australia, the prevalence of MRMM was high overall (63%) and significantly higher in men than in women (81.0% vs. 30.4%, $p<0.0001$). Notably, it was present in 100% of anal swab specimens from men [16], suggesting that the rectum may serve as a reservoir of antibiotic resistant infections. This, along with the strong relationship between macrolide resistance and MSM observed by Barberá and colleagues [4], suggests that MSM may be disproportionately contributing to the increasing prevalence.

Although Chernesky et al did not evaluate markers of quinolone resistance, Barberá and colleagues observed mutations in the *par C* region of the QRDR in 8%, only slightly lower than the 13.6% prevalence of *parC* mutations recently reported by Murray and colleagues in Melbourne, Australia [17]. Recently reported *parC* mutations were somewhat lower in Russia (6.2%) and in Estonia (5.0%), but still significant [14]. Given the speed with which azithromycin resistance has spread, these recent reports of quinolone resistance probably reflect the tip of the iceberg and we can expect them to increase.

Perhaps most concerning is the detection of markers of dual resistance to macrolides and quinolones in 3.6% of tested specimens in Spain [4]. With this, Spain becomes the 5th geographic location in 2017 to report dual resistance and follows case reports from Great Britain [18] and Japan [19], as well as cross-sectional estimates of 1% in Russia and Estonia [14] and 9% in Australia [17]. In contrast to the clear and consistent evidence demonstrating that treatment with azithromycin selects for MRMM, none of the Spanish men with mutations in the QRDR identified by Barberá et al had reported previous treatment with any quinolone in the past 12 months [4]. However, despite this lack of correlation between mutations in the QRDR and prior quinolone therapy, *parC* mutations were more common in Australian patients with than without MRMM [17], suggesting that the emergence of dual

resistance is still somehow related to our current practice of sequential monotherapy with azithromycin followed by moxifloxacin.

Azithromycin and moxifloxacin are the only antimicrobials with efficacy against *M. genitalium* in many settings, and this emergence of dual drug resistance dramatically shrinks our available treatment options. Pristinamycin has been effective in cases of multidrug treatment failure [20], as has spectinomycin in one case [21]. However, neither of these therapies is widely available in all settings. Many are now advocating for dual therapy with two different classes of antibiotics, similar to our current approach for *Neisseria gonorrhoeae*. Yet we currently lack two consistently active antimicrobials for this and a successful dual therapy approach will require the identification of novel antimicrobial agents.

In the absence of good dual therapy options, the recent development of diagnostic tests that incorporate the detection of resistance markers [6, 16] has raised hope that we may be able to curb the spread of antibiotic resistance by more careful, targeted therapy. Higher organism burden may contribute to the development of macrolide resistance [20] and some have advocated for a strategy where cases are first treated syndromically with doxycycline to reduce the organism load, and then provided targeted therapy based on the resistance profile (azithromycin for macrolide sensitive strains or moxifloxacin for macrolide resistant strains). Theoretically, this would slow the development of resistance, but there are no empirical data demonstrating the extent to which this strategy is effective. It merits evaluation, but such a study would require a large number of participants, would be logistically challenging, and is not likely to be completed in the near future. Dual treatment with azithromycin and moxifloxacin together may also slow the development of macrolide resistance in macrolide sensitive strains, but this also has not been tested.

The high levels of antimicrobial resistance reported by Barberá et al [4] and Chernesky et al [5] in this issue, serve as a harbinger of the future unless changes are implemented soon. For far too long, many public health practitioners have been calling both for more widely available diagnostic tests for *M. genitalium* and for novel antimicrobial agents. To date, this has not led to the widespread availability of tests or effective new therapies. Changes to prescribing practices and guidelines come slowly, and in many cases this change comes too slowly. The threshold for sounding the alarm for antibiotic resistance in *N. gonorrhoeae* is treatment efficacy less than 95%. With widespread resistance of 50% for our first line therapy, approximately 10% for our second line therapy in some areas, and increasing reports of dual drug resistance, it is time to sound the alarm for *M. genitalium*. We have no widely available therapies that remain consistently effective, and our options for dual drug therapy are of uncertain efficacy. Testing is finally available in many settings and FDA-approved diagnostic tests appear nearer than they have in recent years. While decisions about screening programs must wait for definitive data demonstrating that detecting and treating *M. genitalium* infections can prevent long term sequelae in women, we can begin to act in other areas. We should begin to routinely test symptomatic individuals for *M. genitalium* and perform tests-of-cure each time we do this. We should establish surveillance mechanisms to monitor antibiotic resistance in *M. genitalium*. And we must support the development and testing of novel therapeutic approaches. In the absence of any action,

antibiotic resistance will continue to spread, prevalence will increase, and the efficacy of available therapies will continue to decline. We cannot afford to wait.

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