Characteristics of *Mycoplasma genitalium* urogenital infections in a diverse patient sample from the United States; results from the Aptima Mycoplasma genitalium Evaluation Study (AMES)

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Running title: *Mycoplasma genitalium* urogenital infections in the United States
Key Words: *Mycoplasma genitalium*; sexually transmitted infection; Aptima; Aptima *Mycoplasma genitalium* Evaluation Study (AMES); epidemiology
Data from a large prospective multicenter clinical validation study of a nucleic acid amplification in vitro diagnostic test for *Mycoplasma genitalium* were analyzed to describe the prevalence of *M. genitalium* infection, risk factors, and disease associations in female and male patients seeking care in diverse geographic regions of the United States. Among 1737 female and 1563 male participants, overall *M. genitalium* prevalence was ~10%, and was significantly higher in persons ages 15-24 compared to ages 35-39 (female: 19.8% vs. 4.7%, OR 5.05 [95%CI:3.01-8.46]; male: 16.5% vs. 9.4%, OR 1.91 [95%CI:1.20-3.02]). The risk for *M. genitalium* infection was higher in black (female: 12.0% vs. 6.8%, OR 1.88 [95%CI: 1.30-2.72]; male: 12.9% vs. 6.9%, OR 2.02 [95%CI:1.38-2.96]) and non-Hispanic (female: 11.2% vs. 6.0%, OR 1.97 [95%CI: 1.25-3.10]; male: 11.6% vs. 6.8%, OR 1.80 [95%CI:1.14-2.85]) study participants. Participants reporting urogenital symptoms had significantly elevated risk of *M. genitalium* infection compared to asymptomatic individuals (female: OR 1.53 [95%CI: 1.09-2.14]; male: OR 1.42 [95%CI:1.02-1.99]). Women diagnosed with vaginitis and cervicitis had higher prevalence of *M. genitalium* than women without those diagnoses, although this was statistically significant only for vaginitis (vaginitis: OR 1.88 [95%CI: 1.37-2.58]; cervicitis: OR 1.42 [95%CI: 0.61-2.96]). A diagnosis of urethritis in men was also significantly associated with *M. genitalium* infection (OR 2.97 [95%CI: 2.14-4.13]). Few characteristics distinguished asymptomatic from symptomatic *M. genitalium infections*. These results from persons seeking care in the United States, suggest that *M. genitalium* infection should be considered in young persons presenting with urogenital symptoms.
INTRODUCTION

Reproductive tract disease syndromes account for substantial health care utilization. Approximately 60% of reproductive age women have gynecologic or obstetric visits each year (1), and the last report of physician office visits for male urethritis was approximately 200,000 annually (2). While sexually transmitted pathogens are not implicated in all of these situations, testing for them is often undertaken as part of the diagnostic assessment. Infection with Neisseria gonorrhoeae and Chlamydia trachomatis in women can result in pelvic inflammatory disease (PID) and serious sequelae including ectopic pregnancy, infertility, and chronic pelvic pain (3). For these reasons annual screening of women under age 25 for these pathogens is recommended as a preventive measure (4). Infection with Mycoplasma genitalium has also been linked with female cervicitis, PID, and preterm delivery (5, 6), as well as with male urethritis (7), but the causal relationship between infection and adverse sequelae in women is not well understood and screening is not currently recommended as some of these associations may be inconsistent (6).

Despite the epidemiologic data indicating association of M. genitalium infection with reproductive tract disease syndromes, incorporating M. genitalium diagnostics into initial clinical assessments of these syndromes has only recently become practical. While a number of nucleic acid amplification tests (NAAT), including research-use only assays and CE-marked assays, have been in use since the early 1990’s, the U.S. Food and Drug Administration (FDA) cleared the first M. genitalium nucleic acid amplification test (NAAT), the Aptima® Mycoplasma genitalium (AMG) assay (Hologic Inc., San Diego, CA), in early 2019, paving the way for more widespread consideration of this organism in clinical care in the U.S. This is important because recommended empiric therapy for these syndromes (6) is sub-optimal for M. genitalium and...
more widely available diagnostic tests will permit clinicians to better target appropriate treatment to the infecting pathogen.

To inform the use of *M. genitalium* NAATs in patient management, we analyzed data from the Aptima *Mycoplasma genitalium* Evaluation Study (AMES), a large prospective multi-center clinical study conducted to evaluate the assay (8). We estimated *M. genitalium* prevalence and evaluated the association of *M. genitalium* infection with reproductive tract symptoms, signs, and diagnoses, in persons seeking care at geographically diverse locations in the United States.

**MATERIALS AND METHODS**

**Study Population and Sample Collection.** Persons with or without genitourinary sexually-transmitted infection (STI) symptoms seen at participating sites were enrolled between July 2017 and April 2018 at 21 U.S. sites located in 6 regions of the country (8). Sexually active men and women at least 14 years of age were eligible. Persons were excluded if they had enrolled previously or had received antibiotics potentially active against *M. genitalium* (macrolides, fluoroquinolones, tetracyclines, or clindamycin) within 21 days of enrollment based on estimated time to clearance (9). Clinicians collected urogenital specimens from eligible consented persons during the routine clinic exam, and recorded reported symptoms, clinical observations, and clinical diagnoses.

All participants provided first void urine and swab specimens with a standardized order of collection. In men, the order was clinician-collected urethral swab, self-collected penile-meatal swab, self-collected urine. In women, self-collected specimens were collected first (urine...
followed by vaginal swab). During a speculum exam, clinicians then collected vaginal and endocervical swab specimens, in that order. All specimens were placed into Aptima tubes containing specimen transport medium and stored fresh (2°C to 30°C) or frozen (≤-20°C) after collection. Specimens were tested first at regional laboratories with the investigational AMG assay on the Panther system, which detects *M. genitalium* 16S RNA, and subsequently frozen and transported to Hologic on dry ice for reference testing. Assay controls, including the strains used, have been previously described in detail (10).

*M. genitalium* infection was defined using a patient infected status (PIS) as previously described (8). This was comprised of results from urethral swab specimens for men and patient-collected vaginal swab specimens for women tested with three validated research-use only alternate transcription-mediated amplification (Alt TMA) assays developed by Hologic. Alt TMA assays targeted unique regions of *M. genitalium* 16S or 23S rRNA (8, 10). If at least two of three Alt TMA assay results were positive, the PIS was considered *M. genitalium*-positive; if two Alt TMA assay results were negative, the PIS was considered *M. genitalium*-negative. In validation studies, assay sensitivity was not affected by the freeze-thaw cycle prior to Alt TMA testing.

Participants were classified as symptomatic if they reported at least one of the following STI symptoms: abnormal genital discharge, genital itching, pain/discomfort during sexual intercourse or during urination, or pain/discomfort in the groin or lower belly. Among asymptomatic persons, the reason for the clinic visit was documented. Clinical diagnoses were made according to the clinic’s standard of care.
Statistical Methods. We estimated prevalence and calculated odds ratios (ORs) and 95% confidence intervals (CIs) (11). Prevalence was tabulated by age, sex, symptom status, race/ethnicity, geographic area, and clinic type. Univariable odds ratios for the association of characteristics with *M. genitalium* were calculated separately by sex. Participants with an unknown PIS due to inconclusive results from reference testing with Alt TMA assays (n=61) and/or samples with invalid or missing investigational assay results (n=82) were excluded from the analyses. We performed multivariable logistic regression and evaluated potential confounding characteristics (age, race, other diagnoses), retaining those that had an appreciable influence on estimates of the relationship between *M. genitalium* and specific clinical diagnoses. Analyses were performed with SAS software (version 9.4; SAS Institute Inc, Cary, NC).

Ethics Approval. Institutional review board approvals were obtained locally by all clinical centers. The study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and Belmont Report and in compliance with the FDA and Good Clinical Practice Guidelines set forth by the International Conference on Harmonization (ICH-E6).

RESULTS

Characteristics of the study population.

Of the 3393 persons enrolled, 3300 (97.3%) non-withdrawn persons who provided specimens were evaluable and included in the analyses of assay performance (8). Of these, 1737 were female and 1563 were male (Table 1). Most women (61.0%) were Black, with 34.0% White and 1.7% Asian. Among men, the race/ethnicity distribution was similar to that of women. Hispanic ethnicity was reported by 21.9% and 21.7% of women and men, respectively. Women ranged in age from 15-74 (median of 29 years, IQR 13 [24-37]). The age range for men was similar (16-
82), but the median age was somewhat higher (median 33; IQR 19 [26-45]). Overall, 43.2% of participants were from the Southeastern US and 31.5% were from the Southwestern US. Sites in the Mid-Atlantic, Midwest, Northeast, and Northwest contributed between 2.0% and 8.7% of participants each. The majority of participants attended clinical research centers (39.2%), high-risk STI clinics (31.4%), or family planning clinics (18.5%). Emergency medicine (3.1%), family medicine/OB-GYN (0.6%), and non-STI public health clinics (7.1%) accounted for a lower proportion of all enrollees.

As previously reported (8), the overall *M. genitalium* prevalence was 10.3%. Prevalence was roughly similar in men and women: 10.1% in women, 10.6% in men.

**Association with sociodemographic characteristics**

*M. genitalium* prevalence was highest in persons 15-24 years (19.8% in women, 16.5% in men; **Table 1**) and lowest in persons ≥50 years (0.7% in women, 2.3% in men). Women age 15-24 were five-fold more likely to have *M. genitalium* infection than women age 35-49 (OR 5.05, 95% CI 3.01-8.46) and men age 15-24 were approximately two-fold more likely to have *M. genitalium* infection than men age 35-49 (OR 1.91, 95% CI 1.20-3.02). *M. genitalium* prevalence was similar in Black women and men (12.0% and 12.9%, respectively) and Black women and men were approximately twice as likely to have *M. genitalium* as White participants (OR women 1.88, 95% CI 1.30-2.72; OR men 2.02, 95% CI 1.38-2.96). In contrast, *M. genitalium* prevalence was lower in Hispanic persons (6.0% and 6.8% in women and men, respectively) and non-Hispanic men and women were approximately twice as likely to have *M. genitalium* as Hispanic persons (OR women 1.97, 95% CI 1.25-3.10; OR men 1.80, 95% CI 1.14-2.85).
M. genitalium prevalence among women was lowest in those attending family medicine/OB-GYN clinics (4.8%) and clinical research centers (6.9%). It ranged between 10% and 13% in family planning clinics, STI clinics, and public health attendees, and was highest in women seeking care in emergency medicine settings (16.7%). Women in those settings were nearly three-fold more likely to have M. genitalium than women attending clinical research centers (OR=2.71; 95% CI 1.03-6.34). In contrast, among men, M. genitalium prevalence was highest in STI clinic settings (16.7%). Men attending family planning clinics were twice as likely (OR=2.00; 95% CI 1.21-3.31) and those attending STI clinics were three times as likely (OR=2.93; 95% CI 1.97-4.36) to have an M. genitalium infection relative to men attending clinical research centers.

**Association with patient-reported symptoms**

Symptoms were reported by 61% of women and 55% of men (Table 2). M. genitalium prevalence in symptomatic women and men was similar (11.6% and 12.0%, respectively) and symptomatic persons were more likely to have M. genitalium than asymptomatic persons (OR women 1.53, 95% CI 1.09-2.14; OR men 1.42, 95% CI 1.02-1.99). Among women, prevalence was highest among those reporting abnormal vaginal odor (14.6%), pain during urination (14.4%), or abnormal vaginal discharge (13.0%), and lowest among those reporting abnormal vaginal bleeding (6.3%). Relative to women who did not report each symptom, women who reported abnormal vaginal odor (OR 1.82, 95% CI 1.31-2.52) and abnormal vaginal discharge (OR 1.67, 95% CI 1.22-2.28) were significantly more likely to have M. genitalium infection.

Among men, prevalence was highest among those reporting penile or urethral discharge (20.4%)
and lowest among those reporting itching or tingling of the penis (7.4%). Penile or urethral discharge was the only symptom significantly associated with *M. genitalium* infection among men (OR 2.77, 95% CI 1.94-3.94).

**Association with clinical signs and diagnoses**

Relatively few clinical signs noted during examination were associated with *M. genitalium* infection (Table 3). Among women, only clinician-observed blisters/sores/bumps/rash/warts in the genital region (OR 3.39, 95% CI 1.72-6.69) and clinician-observed abnormal vaginal odor (OR 1.65, 95% CI 1.16-2.33) were associated with *M. genitalium* infection. Despite a non-significant association between *M. genitalium* infection and abnormal vaginal discharge (OR 1.32, 95% CI 0.97-1.81), diagnoses of vaginitis were significantly more common among *M. genitalium* infected women (OR 1.88, 95% CI 1.37-2.58). Although the risk of a cervicitis diagnosis was somewhat elevated among women with *M. genitalium* infection, this was not statistically significant (OR 1.42, 95% CI 0.61-2.96). Observations of lower abdominal and/or pelvic tenderness in women were infrequent, and not associated with *M. genitalium* infection.

Diagnoses of pelvic inflammatory disease (PID) were even more infrequent, occurring in only 11 women (0.6%). *M. genitalium* infection was detected in 2 of 11 women with PID diagnoses, but the relationship between *M. genitalium* and PID was not statistically significant. Among men, clinical signs of swollen lymph nodes in the groin (OR 2.87, 95% CI 1.42-5.77) and abnormal urethral discharge (OR 2.34, 95% CI 1.61-3.40) were both significantly associated with *M. genitalium* infection. Consistent with this was the significantly increased risk of a urethritis diagnosis among men with *M. genitalium* infection (OR 2.97, 95% CI 2.14-4.13). No other clinical diagnoses were significantly associated with *M. genitalium* infection in men.
In multivariable analyses, the relationships between *M. genitalium* and clinical diagnoses were somewhat attenuated after adjusting for age and race. Among women, the association between *M. genitalium* infection and vaginitis remained statistically significant (Adjusted OR [AOR] 1.54, 95% CI 1.13-2.14). However, the relationship between *M. genitalium* infection and cervicitis (AOR 1.08, 95% CI 0.51-2.26) was no longer present in adjusted analyses. Due to the small number of women with PID, estimates were unstable and multivariable analyses are not presented. Among men, the relationship between *M. genitalium* and urethritis remained statistically significant (AOR 2.50, 95% CI 1.77-3.53).

**Characteristics associated with asymptomatic infection**

Overall, 39% of women and 45% of men were asymptomatic (Table 4). *M. genitalium* prevalence was higher in symptomatic than in asymptomatic women and men in almost all subgroups of the population, consistent with the observed association between *M. genitalium* and urogenital symptoms (Table 2).

The relationship between *M. genitalium* and reported symptoms was only statistically significant in four groups. Symptomatic women who were Black (OR 1.56, 95% CI 1.03-2.35), non-Hispanic (OR 1.49, 95% CI 1.03-2.16), or enrolled at family planning clinics (OR 2.47, 95% CI 1.07-6.40), were significantly more likely to have *M. genitalium* infection than asymptomatic women in those groups. Among men from the Southwest US, *M. genitalium* was significantly higher (OR 2.09, 95% CI 1.09-4.02) in symptomatic than asymptomatic men. No other significant associations with symptom status were identified.
Among asymptomatic participants, reason for the clinic visit was not specified in 15.6% of women and 33.7% of men (data not shown). In participants with a documented reason for the visit, prevalence of *M. genitalium* infection was highest among those seeking care because of known contact with a person with a confirmed or suspected STI (11.6% in women, 13.7% in men). Among women, presenting for STI screening or for testing because of contact to a partner with STI were two- to three-fold more likely to have *M. genitalium* than women presenting to the clinic for a routine pelvic exam, although the latter was not statistically significant (OR screening 2.05, 95% CI 1.07-3.93; OR contact 2.84, 95% CI 0.87-9.24).

**DISCUSSION**

We estimated *M. genitalium* prevalence and disease associations in a large, diverse patient population from broad geographic settings across the U.S. Participants were enrolled in a prospective multicenter clinical performance evaluation study conducted to validate the AMG assay, an FDA-cleared (510k# DEN180047) IVD NAAT (8). Urogenital *M. genitalium* prevalence was approximately 10%, slightly lower than previous reports of mostly symptomatic populations (12, 13), reflecting the mix of symptomatic and asymptomatic persons in our study. Prevalence was higher in younger persons and in those of Black race, or non-Hispanic ethnicity, as well as among women attending emergency medicine clinics. Prevalence of *M. genitalium* was also higher among symptomatic than asymptomatic persons, with significant associations between *M. genitalium* and vaginitis in women and between *M. genitalium* and urethritis among men. Few characteristics differentiated symptomatic from asymptomatic *M. genitalium* infections. In asymptomatic study participants, the only reason for clinic visit that was associated with *M. genitalium* infection was seeking care for screening, and this was true only for women.
The association between *M. genitalium* and young age is consistent with previous reports (14-16). Whereas prevalence was highest in 15-24 year olds overall, age-related prevalence dropped substantially in women 25-34 (from nearly 20% to 9.1%), it was only slightly lower in men 25-34 (16.5% vs. 12.8%). This is somewhat similar to results from the Natsal 3 study, which demonstrated a clear linear decrease in *M. genitalium* prevalence with age in women, but in men the highest prevalence was in the 25-34 years age group (14). This may reflect typical sexual mixing patterns, where young women often have older male partners, and therefore often have higher prevalence of STIs than males of the same age (15).

The association of *M. genitalium* infection with vaginitis is of interest and is perhaps substantiated by the accompanying association with abnormal vaginal odor. This symptom is typically associated with bacterial vaginosis (BV) (17), and vaginal symptoms have not been frequently associated with *M. genitalium* (15). Indeed, a recent study evaluating the syndromic management of vaginal discharge concluded that abnormal vaginal discharge was not a sensitive criterion for capturing *M. genitalium* infection (18). Two other previous studies have reported increased risk of acquiring *M. genitalium* among women with BV (19, 20) and the association with vaginitis observed here may reflect an association with BV, although studies are inconsistent. *Trichomonas vaginalis* (TV), another known cause of vaginitis, has also been associated with *M. genitalium* infection (21-23). Regrettably, neither BV diagnoses nor TV test results were provided in the context of this study, so we were unable to evaluate the extent to which BV or TV might explain this association. In our clinical performance study (8), the sensitivity of the investigational AMG assay was highest in self-obtained vaginal swabs (98.9%).
and lower in endocervical samples (81.5%), and self-obtained vaginal swabs are the preferred sample type. This supports the possibility that *M. genitalium* causes vaginal, as well as cervical infection and this warrants further investigation.

There was no association between clinician-recorded diagnoses of cervicitis and *M. genitalium* after adjustment for race and age, consistent with other studies (24). However, we did not have access to medical records to corroborate these reported diagnoses with objective evidence of cervicitis (e.g., easily induced cervical bleeding, elevated polymorphonuclear leukocyte (PMN) counts). Given the decreased availability of microscopy in many clinics, PMNs are often not quantitated, potentially reducing the specificity of cervicitis diagnoses. In previous studies, the association between *M. genitalium* and cervicitis has been strongest in those that defined cervicitis as \(\geq 30\) PMNs/high-powered field in cervical exudates (25).

PID was rare in this population; it was diagnosed in less than 1% of women, restricting our ability to assess its association with *M. genitalium*. This limitation is not unique to our study. The POPI trial, a large randomized trial of chlamydial screening, observed a similarly low rate of PID (1.6%) (26). Study populations with a higher incidence of PID that provide greater statistical power will be needed to definitively determine the role of *M. genitalium* in PID. Although infrequently observed, the association between *M. genitalium* and swollen inguinal lymph nodes, suggests that *M. genitalium* may cause syndromes other than urethritis in men. However, although *M. genitalium* has been detected in men with epididymitis and in men with proctitis, to date no studies have demonstrated statistically significant associations with these syndromes (27, 28).
While it was not surprising that *M. genitalium* prevalence was high in STI clinics, the highest prevalence of *M. genitalium* in women was observed in those attending emergency medicine clinics. In the U.S., many symptomatic persons attend emergency medicine clinics because they do not have a regular health care provider, often because they lack health insurance. These persons may also be at higher risk of STIs. The relatively higher prevalence in family planning clinic attendees was also somewhat surprising, but may reflect the increasing use of these clinics for a variety of sexual health care needs, including care for symptoms of reproductive tract syndromes and STI screening when STI clinics are not readily accessible, or when these clinics are not the care location of choice. Providers in these clinics may need to have a higher index of suspicion for *M. genitalium* and may consider testing symptomatic women for *M. genitalium* as part of clinical management.

There are a number of strengths and limitations to this study. Strengths include the large sample size as well as the variety of geographic locations and clinic types included. The AMG assay is highly sensitive and specific, resulting in minimal misclassification of *M. genitalium* status (8, 29). The reliance on clinical diagnoses may have resulted in some misclassification of syndrome status, but this reflects the situation in many clinical settings; most do not have the capacity to perform microscopy and speculum exams are becoming increasingly less common. We also did not have access to laboratory results for other common STIs that are associated with the clinical conditions that we evaluated (e.g., *C. trachomatis, N. gonorrhoeae, T. vaginalis, BV*) and therefore could not adjust for these causes of the syndromes that we evaluated. Up to 20% of persons infected with *M. genitalium* are co-infected with another STI pathogen (13). We lacked
information on sex of sex partners, HIV status, and high-risk behaviors, and could not assess their relationship with *M. genitalium* infection. Although antibiotic resistance in *M. genitalium* is of substantial concern, with rates exceeding 60% in many regions of the U.S. (13), this study was not designed to evaluate this. Future surveillance studies of the prevalence and distribution of resistance will be important.

In summary, the prevalence of *M. genitalium* in this study population of high-risk (e.g., reporting symptoms consistent with STI or known contact with person with a confirmed or suspected STI) and low-risk (e.g., asymptomatic individual undergoing routine pelvic examination) individuals was high and associated with many of the same characteristics elucidated in previous reports.

Women seeking care in emergency medicine clinics, women with vaginitis, and men with urethritis were most likely to have *M. genitalium* in this study. Clinicians encountering symptomatic patients in these settings or with these syndromes should consider *M. genitalium* as an etiology.

**ACKNOWLEDGMENTS**

The authors thank the patients for their participation in this study. We thank the AMES Study Group Investigators: Anitra Beasley (Planned Parenthood Gulf Coast), Steven Chavoustie (Segal Institute for Clinical Research, Healthcare Clinical Data Inc.), Douglas Denham (Clinical Trials of Texas, Inc.), Julie Dombrowski (University of Washington), Michael Dunn (Quality Clinical Research Inc.), Christopher Emery (Indiana University), Charlotte A. Gaydos (Johns Hopkins University), Wayne Harper (Wake Research Associate, LLC), Edward W. Hook III (University of Alabama at Birmingham), Christopher Jones (Cooper University), Clifford Kinder (AIDS Healthcare Foundation - Miami), Jeffrey D. Klausner (University of California Los Angeles,
AIDS Healthcare Foundation – Los Angeles), Rebecca A. Lillis (Louisiana State University Health Science Center), Michael Lyons (University of Cincinnati), Lisa E. Manhart (University of Washington), Joseph Miller (Henry Ford Hospital), Mobeen Rathore (University of Florida), Robert Shesser (George Washington University), Dane Shipp (Wake Medical Center for Clinical Research), Timothy Spurrell (Planned Parenthood South New England), Stephanie N. Taylor (Louisiana State University Health Sciences Center), Wayne Trout (Ohio State University), Kimberly Ann Workowski (Emory University), and David Yamane (George Washington University).

LEM has received honoraria, reagents, and test-kits for diagnostic assays from Hologic Inc. CAG has received University research funds from Hologic Inc. for this study and acknowledges receipt of *Mycoplasma genitalium* test research kits from Hologic Inc. for other studies. SNT has received research funds from Abbott, Becton Dickinson, Binx, Hologic Inc., and Roche. EWH has received honoraria from Hologic Inc. and Roche Molecular. RAL reports no conflicts. JDK has received donated research supplies from Hologic Inc. CVR, ML, BM, and DKG are scientists employed by Hologic Inc., the study sponsor and the manufacturer of the diagnostic tests used in this study.

This study was funded by Hologic Inc. CAG is also funded by U54 EB007958, NIBIB, NIH and U-01068613, NIAID, NIH. Hologic Inc. was involved in the study design, data interpretation, and the decision to submit for publication in conjunction with the authors.
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Table 1. Prevalence of *M. genitalium* urogenital infection by sociodemographic characteristic, geographic region, and enrollment clinic type.

| Category                        | Female (n=1737) | Male (n=1563) |
|---------------------------------|-----------------|---------------|
|                                 | n/N             | % (95% CI)    | n/N             | % (95% CI)    |
| **Age (y)**                     |                 |               |                 |               |
| 15-24                           | 88/444          | 19.8 (16.4-23.8) | 47/285          | 16.5 (12.6-21.2) |
| 25-34                           | 19/407          | 4.7 (3.0-7.2)  | 37/394          | 9.4 (6.9-12.7)  |
| ≥50                             | 1/135           | 0.7 (0.1-4.1)  | 7/304           | 2.3 (1.1-4.7)  |
| **Race**                        |                 |               |                 |               |
| White                           | 40/591          | 6.8 (5.0-9.1)  | 37/540          | 6.9 (5.0-9.3)  |
| Black                           | 127/1059        | 12.0 (10.2-14.1) | 125/966        | 12.9 (11.0-15.2) |
| Asian                           | 5/29            | 17.2 (7.6-34.5) | 0/18            | 0.0 (0.0-17.6)  |
| Unknown/other race              | 6/79            | 7.6 (3.5-15.6) | 6/67            | 9.0 (4.2-18.2)  |
| **Ethnicity**                   |                 |               |                 |               |
| Hispanic                        | 23/381          | 6.0 (4.1-8.9)  | 23/339          | 6.8 (4.6-10.0)  |
| Non-Hispanic                    | 151/1347        | 11.2 (9.6-13.0) | 140/1209       | 11.6 (9.9-13.5) |
| **Collection Site (Region)**    |                 |               |                 |               |
| Mid-Atlantic                    | 16/142          | 11.3 (7.1-17.5) | 13/118          | 11.0 (6.6-17.9) |
| Midwest                         | 23/190          | 12.1 (8.2-17.5) | 14/98           | 14.3 (8.7-22.6) |
| Northeast                       | 13/106          | 12.3 (7.3-19.9) | 11/119          | 9.2 (5.2-15.8)  |
| Northwest                       | 0/12            | 0.0 (0.0-24.2)  | 3/53            | 5.7 (1.9-15.4)  |
| Southeast                       | 72/703          | 10.2 (8.2-12.7) | 84/721          | 11.7 (9.5-14.2) |
| Southwest                       | 52/584          | 8.9 (6.9-11.5) | 40/454          | 8.8 (6.5-11.8)  | 0.78 (0.40, 1.51) |
| **Collection Site (Type)**      |                 |               |                 |               |
| Clinical research center        | 43/625          | 6.9 (5.1-9.1)  | 43/671          | 6.4 (4.8-8.5)  |
| Emergency medicine              | 8/38            | 16.7 (8.7-29.6) | 7/53           | 13.2 (6.5-24.8) |
| Family medicine/OB-GYN          | 1/21            | 4.8 (0.8-22.7) | 0.68 (0.02, 4.44) | -     | -   | -   |
| Family planning clinic          | 39/378          | 10.3 (7.6-13.8) | 28/232          | 12.1 (8.5-16.9) | 2.00 (1.21, 3.31) |
| Hospital system high-risk STI clinic | 78/800 | 13.0 (10.5-15.9) | 73/437          | 16.7 (13.5-20.5) | 2.93 (1.97, 4.36) |
### M. genitalium Prevalence

| Category               | Female (n=1737) |               | Male (n=1563) |               |
|------------------------|-----------------|---------------|---------------|---------------|
|                        | n/N             | %             | 95% CI        | Odds Ratio    | n/N | %     | 95% CI        | Odds Ratio    |
| Public health clinic   | 7/65            | 10.8          | (5.3-20.6)    | 1.63 (0.59, 3.89) | 14/170 | 8.2 | (5.0-13.3) | 1.31 (0.70, 2.46) |

NC = not calculable.

1 Symptom status was determined based on patient-reported symptoms.

2 Participants could report multiple responses.

Ethnicity was self-reported as unknown by 9 female and 5 male patients. *M. genitalium* was detected in 2/9 females (22.2%; 95% CI 6.3-54.7; OR 4.45 [0.42, 25.05]) and 2/15 males (13.3%; 95% CI 3.7-37.9; OR 2.11 [0.22, 10.22]).

M-A: MD, NC, Wash. D.C.; MW: IN, MI, NE, OH(2); NE: CT, NJ; NW: WA; SE: AL, GA, FL(3), LA; SW: CA(2), TX(2).
Table 2. Prevalence of urogenital *M. genitalium* infection in patients reporting symptoms of urogenital sexually transmitted infection and association with symptoms.

| Patient-reported urogenital symptoms                      | Female (n=1737) | Odds Ratio$^2$ (95% CI) | Male (n=1563) | Odds Ratio$^2$ (95% CI) |
|-----------------------------------------------------------|-----------------|-------------------------|---------------|-------------------------|
| Any reported symptom                                      | 122/1053 (11.6) | 1.53 (1.09, 2.14)       | 104/866 (12.0) | 1.42 (1.02, 1.99)       |
| Pain/discomfort in groin or lower belly                   | 17/159 (10.7)   | 1.07 (0.63, 1.81)       | 12/149 (8.1)  | 0.72 (0.39, 1.33)       |
| Pain/burning/discomfort during urination                 | 18/125 (14.4)   | 1.55 (0.92, 2.62)       | 39/358 (10.9) | 1.05 (0.72, 1.53)       |
| Pain/discomfort during sexual intercourse                 | 11/106 (10.4)   | 1.03 (0.54, 1.96)       | 8/65 (12.3)   | 1.20 (0.48, 2.59)       |
| Genital blisters/sores/bumps/rash/warts                  | 7/69 (10.1)     | 1.00 (0.38, 2.24)       | 9/94 (9.6)    | 0.89 (0.39, 1.82)       |
| Abnormal vaginal odor                                     | 65/445 (14.6)   | 1.82 (1.31, 2.52)       | -             | -                       |
| Vaginal/vulvar itching or irritation                      | 51/429 (11.9)   | 1.28 (0.90, 1.80)       | -             | -                       |
| Abnormal vaginal bleeding                                 | 4/63 (6.3)      | 0.59 (0.15, 1.63)       | -             | -                       |
| Abnormal vaginal discharge                                | 90/692 (13.0)   | 1.67 (1.22, 2.28)       | -             | -                       |
| Penile/urethral discharge                                 | -               | -                       | 56/275 (20.4) | 2.77 (1.94, 3.94)       |
| Burning/itching around opening of penis                   | -               | -                       | 22/269 (8.2)  | 0.72 (0.45, 1.15)       |
| Itching/tingling on the inside of penis                   | -               | -                       | 13/175 (7.4)  | 0.65 (0.36, 1.18)       |

$^1$ Participants could report multiple symptoms.

$^2$ Referent category in all cases is absence of the symptom.
| Clinician-reported urogenital signs | Female (n=1737) | Odds Ratio^2 (95% CI) | Male (n=1563) | Odds Ratio^2 (95% CI) |
|-----------------------------------|-----------------|-----------------------|---------------|-----------------------|
| Any sign of urogenital infection   | 115/1034 (11.1) | 1.32 (0.95, 1.83)     | 77/608 (12.7) | 1.43 (1.03, 1.98)     |
| Swollen lymph nodes in groin       | 0               | NC                    | 11/45 (24.4)  | 2.87 (1.42, 5.77)     |
| Genital blisters/sores/rash/warts | 12/45 (26.7)    | 3.39 (1.72, 6.69)     | 11/135 (8.1)  | 0.74 (0.39, 1.39)     |
| Abnormal vaginal odor             | 51/361 (14.1)   | 1.65 (1.16, 2.33)     | -             | -                     |
| Abnormal vaginal discharge         | 98/858 (11.4)   | 1.32 (0.97, 1.81)     | -             | -                     |
| Clear                             | 6/58 (10.3)     | Reference             | -             | -                     |
| White                             | 58/536 (10.8)   | 1.05 (0.43, 3.13)^3   | -             | -                     |
| Pink, bloody, brown, gray, other  | 18/156 (11.5)   | 1.13 (0.40, 3.67)^3   | -             | -                     |
| Yellow, green (pus-like)          | 16/108 (14.8)   | 1.51 (0.52, 4.99)^3   | -             | -                     |
| Urethral erythema                  | 0               | NC                    | 17/207 (8.2)  | 0.73 (0.43, 1.23)     |
| Abnormal urethral discharge        | 1/16 (6.3)      | 0.59 (0.01, 3.87)     | 46/244 (18.9) | 2.54 (1.61, 3.60)     |
| Lower abdominal/pelvic tenderness  | 1/35 (2.9)      | 0.26 (0.01, 1.55)     | 0             | 0                     |
| Pain or swelling of testicles      | -               | -                     | 3/25 (12.0)   | 1.16 (0.22, 3.92)     |
| Clinician’s Diagnosis^4            |                 |                       |               |                       |
| Any clinical finding               | 122/1024 (11.9) | 1.65 (1.18, 2.31)     | 103/755 (13.6) | 1.90 (1.36, 2.65)     |
| Cervicitis                        | 9/66 (13.6)     | 1.42 (0.61, 2.96)     | -             | -                     |
| Pelvic inflammatory disease        | 2/11 (18.2)     | 1.98 (0.21, 9.68)     | -             | -                     |
| Vaginitis                         | 101/752 (13.4)  | 1.88 (1.37, 2.58)     | -             | -                     |
| Cystitis                          | 1/13 (7.7)      | 0.74 (0.02, 5.04)     | 0             | 0                     |
| Urethritis                        | 0/2 (0.0)       | NC                    | 83/438 (18.9) | 2.97 (2.14, 4.13)     |
| Abdominal/pelvic pain             | 2/17 (11.8)     | 1.18 (0.13, 5.16)     | 0             | NC                    |
| Genital lesions                   | 0/4 (0.0)       | NC                    | 1/12 (8.3)    | 0.77 (0.02, 5.35)     |
| Genital warts                     | 1/2 (50.0)      | 8.91 (0.11, 700.16)   | 4/31 (12.9)   | 1.26 (0.32, 3.69)     |
| Urinary tract infection           | 0/16 (0.0)      | NC                    | 0             | NC                    |
| HSV                               | 3/13 (23.1)     | 2.69 (0.47, 10.57)    | 0             | NC                    |
| Other^4, Not available, Unknown   | 13/186 (7.0)    | 0.64 (0.36, 1.15)     | 15/264 (5.7)  | 0.46 (0.27, 0.80)     |

NC = not calculable.

^1 Clinician could report multiple signs or diagnoses.

^2 Unless otherwise noted, referent category is absence of the sign or diagnosis.

^3 Referent is clear abnormal vaginal discharge.

^4 Includes balanitis, proctitis, lymphadenopathy.
Table 4. Characteristics associated with asymptomatic urogenital *M. genitalium* infection.

| Category | Sym<sup>1</sup> (% (n/N)) | ASym<sup>1</sup> (% (n/N)) | Odds Ratio<sup>2</sup> (95% CI) | Sym<sup>1</sup> (% (n/N)) | ASym<sup>1</sup> (% (n/N)) | Odds Ratio<sup>2</sup> (95% CI) |
|----------|---------------------------|---------------------------|-------------------------------|---------------------------|---------------------------|-------------------------------|
| Age (y)  |                           |                           |                               |                           |                           |                               |
| 15-24    | 21.4 (65/304)             | 16.4 (23/140)             | 1.38 (0.82, 2.34)             | 18.8 (30/160)             | 13.6 (17/125)             | 1.47 (0.77, 2.80)             |
| 25-34    | 10.2 (46/452)             | 7.4 (22/299)              | 1.43 (0.84, 2.42)             | 14.9 (46/309)             | 10.3 (28/271)             | 1.52 (0.92, 2.51)             |
| 35-49    | 4.0 (10/247)              | 5.6 (9/160)               | 0.71 (0.25, 2.02)             | 11.7 (25/213)             | 6.6 (12/181)              | 1.87 (0.91, 3.84)             |
| ≥50      | 2.0 (1/50)                | 0.0 (0/85)                | Inf (0.09, Inf)               | 1.6 (3/184)               | 3.3 (4/120)               | 0.48 (0.07, 2.90)             |
| Race<sup>3</sup> |                    |                           |                               |                           |                           |                               |
| White    | 7.4 (23/310)             | 6.0 (17/281)             | 1.24 (0.65, 2.38)             | 8.5 (22/259)             | 5.3 (15/281)             | 1.65 (0.83, 3.25)             |
| Black    | 13.6 (92/677)             | 9.2 (35/382)             | 1.56 (1.03, 2.35)             | 13.9 (81/584)             | 11.5 (44/382)             | 1.24 (0.84, 1.83)             |
| Asian    | 23.8 (5/21)               | 0.0 (0/8)                | Inf (0.49, Inf)               | 0.0 (0/9)                | 0.0 (0/9)                | NC                            |
| Unknown/other race | 7.0 (4/57)             | 9.1 (2/22)               | 0.75 (0.10, 8.99)             | 7.7 (2/41)              | 3.3 (1/34)               | 1.65 (0.20, 13.30)            |
| Ethnicity<sup>4</sup> |                  |                           |                               |                           |                           |                               |
| Hispanic | 6.7 (14/210)             | 5.3 (9/171)              | 1.29 (0.50, 3.46)             | 7.3 (12/164)             | 6.3 (11/175)             | 1.18 (0.50, 2.75)             |
| Non-Hispanic | 12.6 (106/838)          | 8.8 (45/509)             | 1.49 (1.03, 2.16)             | 13.0 (90/694)            | 7.5 (50/515)             | 1.39 (0.96, 2.00)             |
| Collection Site (Region)<sup>5</sup> |                     |                           |                               |                           |                           |                               |
| Mid-Atlantic | 13.2 (9/88)             | 9.5 (7/74)               | 1.46 (0.45, 4.91)             | 11.7 (9/77)              | 9.8 (4/41)               | 1.22 (0.31, 5.81)             |
| Midwest   | 12.1 (17/141)            | 12.2 (6/49)              | 0.98 (0.34, 3.24)             | 13.2 (7/53)              | 15.6 (7/45)              | 0.83 (0.23, 3.04)             |
| Northeast | 12.7 (9/71)              | 11.4 (4/35)              | 1.13 (0.29, 5.39)             | 12.9 (4/31)              | 8.0 (7/88)               | 1.71 (0.34, 7.34)             |
| Northwest | 0.0 (0/0)                | 0.0 (0/0)                | NC                            | 6.4 (3/47)               | 0.0 (0/6)                | Inf (0.07, Inf)               |
| Southeast | 11.8 (54/459)            | 7.4 (18/244)             | 1.67 (0.96, 2.92)             | 12.1 (60/494)            | 10.6 (24/227)            | 1.17 (0.71, 1.93)             |
| Southwest | 10.8 (33/305)            | 6.8 (19/279)             | 1.66 (0.92, 2.99)             | 12.8 (21/164)            | 6.6 (19/290)             | 2.09 (1.09, 4.02)             |
| Collection Site (Type) |                   |                           |                               |                           |                           |                               |
| Clinical research center | 6.6 (19/287)            | 7.1 (24/338)             | 0.93 (0.50, 1.73)             | 6.0 (23/383)            | 6.9 (20/288)             | 0.86 (0.46, 1.59)             |
| Emergency medicine | 15.2 (7/46)             | 50.0 (1/2)               | 0.18 (0.00, 16.09)            | 15.2 (7/46)             | 0.0 (0/7)                | Inf (0.27, Inf)               |
| Family medicine/OB-GYN | 0.0 (0/5)                | 6.3 (1/16)               | NC                            | 13.0 (31/238)            | 5.7 (8/140)              | 2.47 (1.07, 6.40)             |
| Family planning clinic | 13.0 (31/238)            | 5.7 (8/140)              | 2.47 (1.07, 6.40)             | 16.3 (15/92)             | 9.3 (13/140)             | 1.90 (0.86, 4.21)             |
| Hospital system high-risk STI clinic | 13.7 (62/452)            | 10.8 (16/148)            | 1.31 (0.73, 2.35)             | 17.6 (51/289)            | 14.9 (22/148)             | 1.23 (0.71, 2.12)             |
| Public health clinic | 12.0 (3/25)             | 10.0 (4/40)              | 1.23 (0.16, 7.99)             | 14.3 (8/56)             | 5.3 (6/114)              | 3.00 (0.85, 11.03)             |
Symptom status is determined based on patient-reported symptoms. Odds ratio represents the association of *M. genitalium* with symptoms in each subgroup. Referent category in all cases is asymptomatic participants. Participants could report multiple responses. *M. genitalium* was detected in 2/5 symptomatic female participants (40%; OR Inf [0.24-Inf], and 2/8 symptomatic male participants (25%, OR Inf [0.26-Inf]) who self-reported ethnicity as unknown.