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Should we be testing for *Mycoplasma genitalium* on initial presentation? Trends in persistent/recurrent urethritis among men presenting for care in STD clinics, 2015–2019, STD Surveillance Network (SSuN)

Eloisa Llata, MD, MPH[1], **Erin Tromble, MD**[1], **Christina Schumacher, PhD**[2], **Dawn Huspeni, MPH**[3], **Lenore Asbel, MD**[4], **Preeti Pathela, DrPH**[5], **Robert Kohn, MPH**[6], **Roxanne P. Kerani, PhD**[7], **Lindley Barbee, MD, MPH**[1,*], **Laura Bachman, MD, MPH**[1,*]

[1]Centers for Disease Control and Prevention, Division of STD Prevention (NCHHSTP)

[2]Johns Hopkins University School of Medicine and Baltimore City Health Department, Baltimore, Maryland

[3]Minnesota Department of Health, Minneapolis/St. Paul, Minnesota

[4]Philadelphia Department of Public Health, Philadelphia, Pennsylvania

[5]New York City Department of Health & Mental Hygiene, New York City, New York

[6]San Francisco Department of Public Health, San Francisco, California

[7]Public Health – Seattle and King County and Department of Medicine, University of Washington, Seattle, Washington

Abstract

Background—*Mycoplasma genitalium* is a major contributor to persistent/recurrent urethritis cases. However, there are limited published studies on recent trends of persistent/recurrent urethritis.

Methods—A retrospective analysis was conducted of men presenting with symptomatic urethritis in 16 STD clinics from 2015–2019. Poisson regression was used to assess trends in the annual proportions of urethritis episodes with follow-up (FU) characterized with persistent/recurrent urethritis symptoms. Results were also stratified by results of chlamydia (CT) and gonorrhea (NG) testing and treatment prescribed.

Results—There were 99,897 urethritis episodes, from 67,546 unique men. The proportion of episodes with persistent/recurrent symptomatic FU visits increased 50.8% over a 4-year period (annual percentage change (APC) 11.3%, 95% CI, 6.5–16.3). Similar trends were observed in non-chlamydial non-gonococcal urethritis episodes(APC, 12.7%; 95% CI, 6.8–18.9) but increases

Correspondence Eloisa Llata, 1600 Clifton Rd. MS H24-4, Atlanta, GA 30329, USA, Fax Number: 404-639-4030, gge3@cdc.gov.
*Co-senior authors

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among those positive for NG (APC, 12.1%; 95% CI, −2.3 −28.5) or for CT (APC, 7.3%; 95% CI, −6.7–23.5) were not statistically significant. Among episodes who received azithromycin as first-line treatment, increases in the proportion of persistent/recurrent FU visits were observed (APC, 12.6%; 95% CI, 8.6–16.7). For episodes where first-line treatment was doxycycline, no significant increases were detected (APC, 4.3%; 95% CI, −0.3–9.2).

Conclusion—We found an increase in the proportion of urethritis episodes with persistent or recurrent symptoms over time. Given these observed trends in episodes negative for NG or CT, an etiology not detectable by routine diagnostics was a likely factor in increased persistence, suggesting patients with urethritis may benefit from diagnostic testing for *M. genitalium* during an initial symptomatic presentation.

Summary:

In this trend analysis we report an increase in the proportion of men with urethritis who experienced persistence or recurrence among a sentinel population of men attending US STD clinics.

Keywords

urethritis; *Mycoplasma genitalium* ; STD clinics

Introduction

Mycoplasma genitalium is a common cause of persistent/recurrent non-gonococcal urethritis, accounting for more than 40% of all persistent/recurrent cases when a pathogen is identified [1–3]. Although *M. genitalium* was first identified over 40 years ago [4], it was not until 2015 that it was characterized as an emerging issue in the STD Treatment Guidelines published by the United States Centers for Disease Control and Prevention (CDC) [5]. Since its discovery, *M. genitalium* has been identified as the causative agent of up to 15–30% of non-gonococcal urethritis [2,6–11], often as a coinfection with *Chlamydia trachomatis*. However, this latter correlation has been noted in some studies[12–14] but absent in another [15], potentially supporting an independent role of *M genitalium* in urethritis.

Antimicrobial resistance (AMR) has been increasing among *M. genitalium.* Between 2010 and 2017 the prevalence of macrolide resistant *M. genitalium* in the U.S. increased from 10% to >50% [16]. Fluoroquinolone resistance has also been increasingly detected [7–8]. In 2019, the bacterium was added to the CDC Antibiotic Resistance Threats watch list [17]. Until 2021, a macrolide, azithromycin, was the recommended first-line therapy for non-gonococcal urethritis by the CDC [5], and it was not until 2019 that the first US Food and Drug Administration (FDA) authorized nucleic acid amplification test (NAAT) was approved for the clinical diagnosis of *M. genitalium* [18]. However, the CDC only recommends using the *M. genitalium* NAAT for persistent/recurrent urethritis [11] potentially due to concerns about treatment potentially driving the development of antimicrobial resistance and a lack of evidence that macrolide-resistant *M. genitalium* is causing increases in persistent/recurrent urethritis.

Given a strong association between *M. genitalium* and persistent/recurrent urethritis and that antimicrobial resistant *M. genitalium* is increasing, one might expect increases in the trends of recurrent or persistent urethritis at the population level. However, to date, there are no published studies on the recent trends of persistent/recurrent urethritis. To address this gap, we analyzed data collected via CDC's STD Surveillance Network (SSuN) to assess trends in persistent/recurrent urethritis among men presenting to urban, high volume sexual health clinics over time.

Materials and Methods

Design and setting

We conducted a retrospective cross-sectional analysis utilizing data from the STD Surveillance Network (SSuN), a sentinel STD surveillance project funded by the CDC (CDC, PS13–1306), where 10 state, local and county health departments conduct facility-based surveillance in publicly-funded, urban STD clinics. Data on all patients presenting for care, regardless of diagnosis, are collected as part of routine medical care. Patient-level data are deidentified and extracted from clinics' electronic databases and transmitted to CDC by collaborating health departments.

We used data from January 1, 2015, through December 31, 2019, to analyze annual trends in the proportion of men with symptoms consistent with urethritis who repeatedly presented to the clinic with persistent/recurrent symptoms. Although the CDC defines urethritis as ≥2 polymorphonuclear (PMN) cells per high power field (HPF) on Gram-stain microscopy of either a urethral swab or first-void urine sample, due to data limitations, we defined urethritis as men presenting with complaints of either urethral discharge and/or dysuria (e.g., symptomatic). Of the 10 jurisdictions funded for SSuN, we included 16 STD clinics for which visit-level data on either reported or denied dysuria/discharge were provided. This included the following 7 jurisdictions: Baltimore, Maryland (2 clinics), Minneapolis, Minnesota (1 clinic), Multnomah County, Oregon (1 clinic), Philadelphia, Pennsylvania (2 clinics), New York City, New York (8 clinics), San Francisco, California (1 clinic), and Seattle, Washington (1 clinic). All sites contributed data throughout the entire study period except for Minnesota, whose data went through September 30, 2019, and Seattle for whom 2015 data was not available.

Data Collection

As part of the SSuN project, sites regularly transmit a collaboratively identified set of data elements for all patients seeking sexual health services at participating STD clinics. We examined the following data for our study: gender, age, race/ethnicity, symptoms, HIV status, gender of sexual contacts and/or self-identified sexual orientation, anatomic site-specific chlamydia (CT) and gonorrhea (NG) testing and results, STD diagnoses, and treatment provided/prescribed. Age was analyzed by age group (≤19, 20–24, 25–34, 35–44, ≥45 years) at patients' initial symptomatic visit. We defined men who either reported male sexual partners or identified as homosexual or bisexual at any of their patient visits in the medical record as gay, bisexual, and other men who have sex with men [referred to as MSM]. Men who reported only female sexual partners and/or identified as heterosexual

were classified as men who have sex with women only [MSW] and those whose gender of sexual partners or sexual orientation were not documented were classified as men with sexual partners of unknown gender (M_{UNK}). Laboratory diagnosis of gonorrhea and chlamydia primarily included NAAT assays. However, 5 of the 8 jurisdictions provided data on gram stain, including negative or positive results based on the presence of gram-negative diplococci. Laboratory data on trichomonas was not available. Treatment data were reviewed for the following antimicrobials if provided or prescribed on or within 14 days of the initial testing visit: amoxicillin, azithromycin, ceftriaxone, clindamycin, cefixime, cefotaxime, doxycycline, erythromycin, gentamicin, levofloxacin, moxifloxacin, and ofloxacin. Although treatment data were collected, the full dosing schedule was not always available, and hence we only included the specific drugs in the following categories: azithromycin (alone or in combination with another antimicrobial), doxycycline (alone or in combination with other non-azithromycin antimicrobials), and other (prescribed antimicrobial(s) that did not include azithromycin nor doxycycline).

Data Analysis

Creation of episodes—The unit of our analysis was a urethritis episode. The first visit where a male presented with dysuria and/or discharge and was tested for urethral CT and NG occurring January 1, 2015, to November 2019 (August 2019 for Minnesota) was designated as the start or the “index visit” for that episode. The end of the episode was 45 days from the index visit for patients who were treated on the index visit and for patients who did not have a treatment record associated within 14 days of the index visit. If a treatment record was associated within 14 days but not on the index visit, the end of the episode was 45 days after the date the treatment was provided or prescribed. We reviewed all clinical encounters within the episode window (45 days) and defined persistent/recurrent urethritis if the patient returned for a follow up visit(s) with complaints of dysuria or discharge. For this study, we chose a 45-day endpoint to allow for sufficient time between initial evaluation and any visits where a patient might be reassessed for resolution of initial symptoms. Unique patient and visit identifiers fere used to identify multiple visits for a given patient and a single line of data was created for each urethritis episode. Subsequent symptomatic visits with urethral CT/NG testing for a given patient became a new episode if they were at least 45 days after the index event or from when treatment was provided/prescribed. A patient could contribute more than one episode to the dataset during the 5-year period. Among those episodes with symptomatic and/or asymptomatic FU visits, the patterns were described as either consecutive (having only sequential symptomatic visits or sequential symptomatic visits followed only by 1 or more asymptomatic visits) or non-consecutive (having asymptomatic visits in between symptomatic visits).

Statistical Analysis—The primary analysis consisted of evaluating trends in the proportion of episodes of men diagnosed with urethritis with persistent/recurrent symptomatic visits. Annual proportions were determined for each jurisdiction, and a generalized estimating equations approach was applied to account for the correlations between repeated measurements within the same jurisdiction. The annual number of persistent/recurrent episodes were modeled as Poisson counts and the natural log of the total annual episodes was included as the model offset to estimate annual proportions.

We specified an exchangeable working correlation structure with random intercepts for the jurisdictions. The annual percent change (APC) was estimated from the regression coefficient for the year of the episode while controlling for SSuN jurisdictions. This Poisson model was also used to assess statistical significance in trends in the proportion over time, stratified by pathogen at index presentation and treatment provided/prescribed with appropriate denominator populations. An APC is statistically significant when its 95% CI does not cross zero. Analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

During the 5-year observation period, there were 591,890 male patient visits across 16 SSuN STD clinics, representing 241,290 unique male patients. After the creation of the episodes described above, our final analytic cohort included 99, 897 episodes of urethritis. There were 18,287 episodes in 2015, 17,827 in 2016, 18,509 in 2017, 23,325 in 2018, and 21,949 in 2019. Most episodes were among men presenting with discharge at the initial visit (n=96,550) either alone (43,261/96,550 or 44.8%) or discharge plus dysuria (53,289/96,550 or 55.2%). The remainder presented with dysuria only (3,347 or 3.4%). Descriptive characteristics for both unique men and episodes are presented in Table 1. The number of episodes varied by jurisdiction with New York City contributing over half of the episodes (n= 55,736 or 55.8%) and Multnomah County contributing the least number of episodes (n= 2,560 or 2.6%) during the 5-year time frame. The episodes were among 67,546 unique patients, most of whom had only 1 episode (n= 50,192 or 74.3%), followed by 15.1% (n=10,166) who had 2 episodes, and 10.6% (n= 7,188) with 3–19 episodes. Nearly half of the men (46.3%) were non-Hispanic Black and approximately one quarter were non-Hispanic White (24.3%). Many of the men were between 25–44 years old (64.3%) and were MSW (60.5%).

Most of the episodes (77,327/99,897 or 77.4%) occurred without any subsequent FU visits within the 45-day time frame. Another 14,337 or 14.4% episodes were among men who did have follow-up visits within the 45-day timeframe but were asymptomatic at all those visits. The remaining 8,233 (8.2%) episodes were among men who reported persistent dysuria and/or discharge in ≥1 of their FU visits. The majority (90.7%) of these episodes had consecutive symptomatic follow-up visits (Figure 1). From 2015 to 2019, the annual proportion of persistent or recurrent urethritis episodes increased 50.8%, from 6.3% in 2015 to 9.5% in 2019 (APC 11.3%, 95% CI, 6.5–16.3) (Figure 2). However, we observed variations across jurisdictions where the least proportion of episodes with persistent/recurrent symptoms was in Multnomah County, OR, and the highest proportion was in Minneapolis, MN (see Table, Supplemental Digital Content 1, which displays SSuN site-specific proportions).

Of the 99,897 episodes, 17,146 (17.2%) episodes were NG NAAT positive and/or Gram stain positive suggestive of NG (14,245 NG only and 2,901 CT and NG) and 10,559 (10.6%) episodes NAAT positive for CT only. Episodes among men with symptomatic FU visits who tested positive for NG increased over time, but the trend was not statistically significant (APC, 12.1%; 95% CI, −2.3–28.5) (Figure 3a-c). Episodes of men who tested CT positive

only also increased over time, with non-statistically significant trends observed (APC, 7.3%; 95% CI, −6.7–23.5) (Figure 3a-c). In addition, episodes of men with urethritis negative for both CT and NG with symptomatic FU visits increased significantly from 5.9% in 2015 to 9.2% in 2019 (APC, 12.7%; 95% CI, 6.8–18.9) (Figure 3a-c).

Of the 99,897 episodes, 71,410 (71.5%) were associated with ≥1 treatment record on or within 14 days of the initial testing visit. Of those, most episodes were treated with an azithromycin-based regimen (n=65,163; 91.3%), followed by those associated with doxycycline-based regimen(n= 5,885; 8.2%), and other prescribed non-azithromycin/non-doxycycline antimicrobials (n=362; 0.4%). The proportion of symptomatic FU visits among men treated with azithromycin increased significantly from 7.4% in 2015 to 11.7% in 2019 (APC, 12.6%; 95% CI, 8.6–16.7) (Figure 4a-b). In contrast, the proportion of those episodes with symptomatic FU visits treated with doxycycline regimens increased slightly from 7.0% in 2015 to 8.2% in 2019 (APC, 4.3%; 95% CI, −0.3–9.2), though not statistically significant (Figure 4a-b). Significant trends were also observed among episodes of patients diagnosed with CT and non-chlamydial non-gonococcal urethritis (NCNGU) who were prescribed azithromycin increasing from 7.7% in 2015 to 12.8% in 2019 (APC, 7.7%; 95% CI, 7.6 – 20.2) but not for those prescribed doxycycline (7.5% in 2015 to 7.9% in 2019)(APC, 7.5%; 95% CI, −3.6 – 9.3).

Discussion

Over a 5-year period from 2015 to 2019, we found a significant increase in the overall proportion of men visiting high volume sexual health clinics with multiple symptomatic visits related to a single episode of urethritis, suggesting a rise in the proportion of men with urethritis who experienced persistence or recurrence. Most importantly, this same trend was identified for NCNGU episodes and for episodes treated with azithromycin but not doxycycline. The retrospective nature of our study did not allow us to determine the specific etiology underlying patients' ongoing symptoms, and the lack of availability of an FDA-approved test for *M. genitalium* until the final year of the study-period also prevented direct assessment of the degree to which *M. genitalium* was responsible for persistent symptoms. However, the consistent increase in persistent/recurrent follow up visits, observed most strongly in the absence of gonorrhea or chlamydia suggests an etiology not detectable by routine diagnostics was a likely factor in increased persistence – both as a sole etiology and as a source of coinfection. Given the role *M. genitalium* is now known to play in individual cases of both coinfection [12–15] and persistent/recurrent urethritis [9–11], *M. genitalium* may be the primary driver of the changes we observed during the study period.

Interestingly, men who received azithromycin – widely used as first line treatment for NGU during the period captured by our study [5, 19] – also demonstrated evidence of increased persistent/recurrent urethritis. However, men treated with doxycycline did not experience this increase. The former suggests decreased efficacy of azithromycin against *M. genitalium* over time and may be consistent with other published studies that found wide use of azithromycin may have contributed to *M. genitalium*'s resistance and declining NGU cure rates [20–22]. One possible explanation for this finding is that use of azithromycin may have resulted in incomplete or failed treatment of undetected *M. genitalium* [9, 23]

due to pre-existing macrolide-resistance. It is also possible that the use of azithromycin contributed to the development of antimicrobial resistance particularly given azithromycin's long half-life [24] and *M. genitalium's* slow growth cycle [2]. The CDC now recommends doxycycline as opposed to azithromycin for first-line treatment of NGU due to evidence of macrolide-related treatment failure and increasing rates of antimicrobial resistance [11]. Our results add further evidence in support of this change.

Our findings should be put in context of a recently published study by Johnson, et al in San Francisco. The authors conducted a pre-post analysis following the implementation of routine *M. genitalium* testing at initial presentation of non-gonococcal urethritis in a high-volume sexual health clinic. Patients positive for *M. genitalium* received moxifloxacin for 7 days following empiric treatment with 7 days of doxycycline. With this approach, they found a statistically significant decrease in persistent NGU (8% vs. 3%, $p<0.001$) among men seeking care [24]. Given the rising rates of persistent/recurrent urethritis as we found, the San Francisco strategy to test for *M. genitalium* at initial presentation may help decrease persistent/recurrent urethritis at the population level.

There were several limitations to our study. In addition to the previously noted inability to determine the specific etiology underlying patients' persistent/recurrent symptoms, we were also unable to distinguish between patients with persistent/recurrent urethritis versus those experiencing reinfection. However, while intermittent changes in the proportion of men with reinfection may be expected, changes in pathogen characteristics such as rising AMR are a plausible explanation for the consistent increases, we identified over time. An additional limitation is that the definition of urethritis was constructed using self-reported symptoms of dysuria and discharge as SSuN did not collect all the variables necessary for the diagnostic criteria of urethritis. However, discharge and dysuria have been significantly associated with urethritis and have been shown to be present in most urethritis cases [25]. Finally, the study sample was limited to a cohort of men attending high volume sexual health clinics participating in CDC's STD Surveillance Network, and thus the results may not be generalizable beyond this context. Nevertheless, our results provide evidence that persistent urethritis is a rising concern among certain populations.

We identified an increase in the proportion of men with urethritis who experienced persistence or recurrence among a sentinel population of men presenting to high volume sexual health clinics from 2015 to 2019. These results provide evidence of increases in persistent/recurrent urethritis over time, and with the understanding that persistent/recurrent urethritis with an identifiable pathogen may be due to *M. genitalium*, suggests that macrolide-resistant *M. genitalium* may be driving this increase. With recent data demonstrating that initial identification of *M. genitalium* and effective treatment among men presenting with urethral symptoms resulted in a decrease in persistent/recurrent NGU, our results suggest that males may benefit from diagnostic testing for *M. genitalium* during the initial symptomatic presentation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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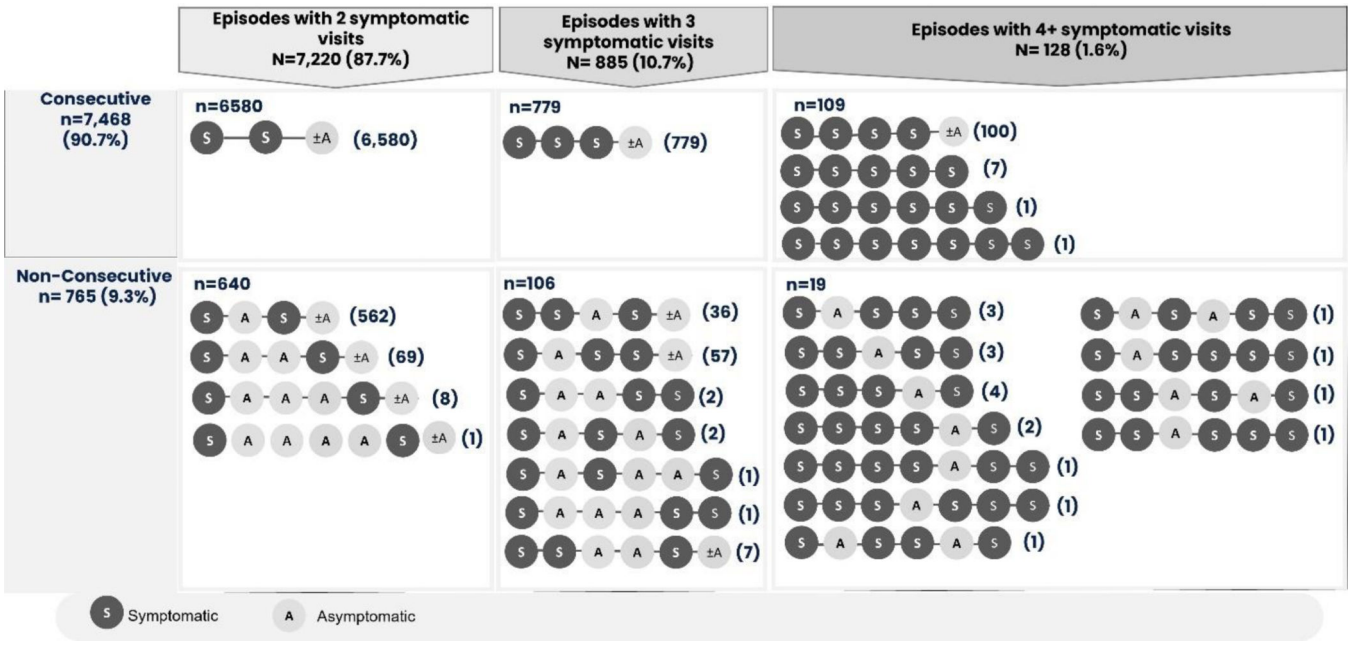

Figure 1.

Sequence of symptomatic*and asymptomatic visits among urethritis episodes (n=8,233) of men with persistent/recurrent† urethritis, 2015−2019, STD Surveillance Network

*Includes dysuria and/or discharge.

†Defined as episodes with ≥1 follow-up visits during the episode window of 45 days where the patient continues to report dysuria and/or discharge.

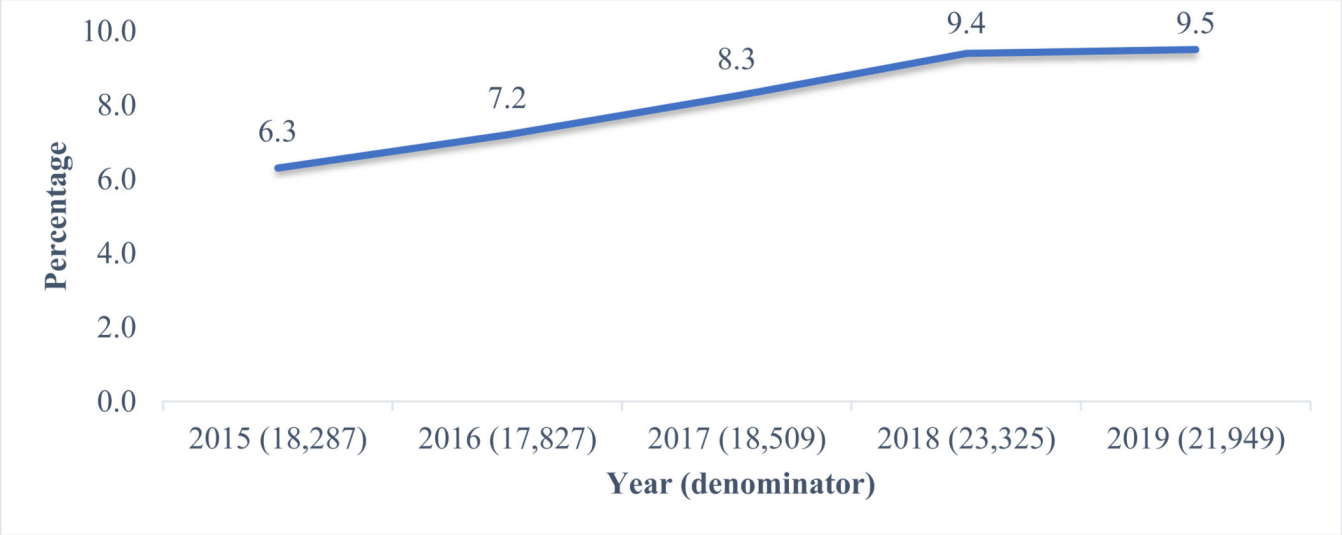

Figure 2.

Overall trends in the proportion of urethritis episodes (n = 99,897) of men with persistent/recurrent symptoms*, 2015−2019, STD Surveillance Network

*Includes dysuria and/or discharge.

Note: To examine temporal trends, we used Poisson regression, which fits trend date to identify significant trends in annual prevalence of urethritis episodes with persistent/recurrent urethritis (i.e., follow-up visits where patient complained of dysuria and/or discharge) while controlling for SSuN jurisdictions (APC 11.3%, 95% CI, 6.5–16.3).

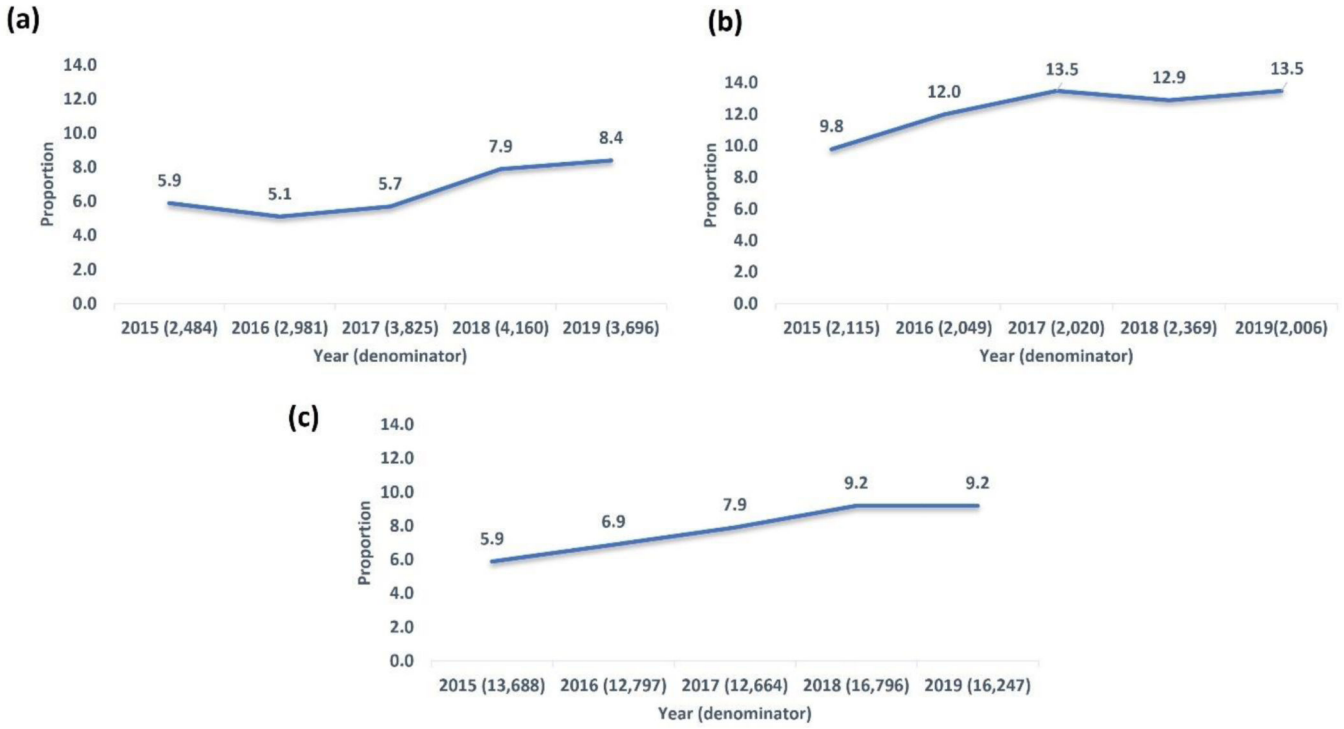

Figure 3a-c.

Trends in the proportion of episodes of men diagnosed with urethritis who had ≥1 symptomatic* follow-up visits† from 2015−2019 by (a) among those positive for gonorrhea‡ (n=17,146), (b) among those positive for chlamydia only (n= 10,559), and (c) among non-gonococcal non-chlamydial only (n=72,192), STD Surveillance Network

*includes dysuria and/or discharge; †within 45 days of initial presentation; ‡includes both NAAT NG and gram stain positive results

Note: Poisson model was also used to assess statistical significance in trends in the proportion over time estimating the annual percent change from the regression coefficient for the year of the episode. (a) APC, 12.1%; 95% CI, −2.3% to 28.5%; (b) APC, 7.3%; 95% CI, −6.7% to 23.5%; (c) APC, 12.7%; 95% CI, 6.8% to 18.9%.

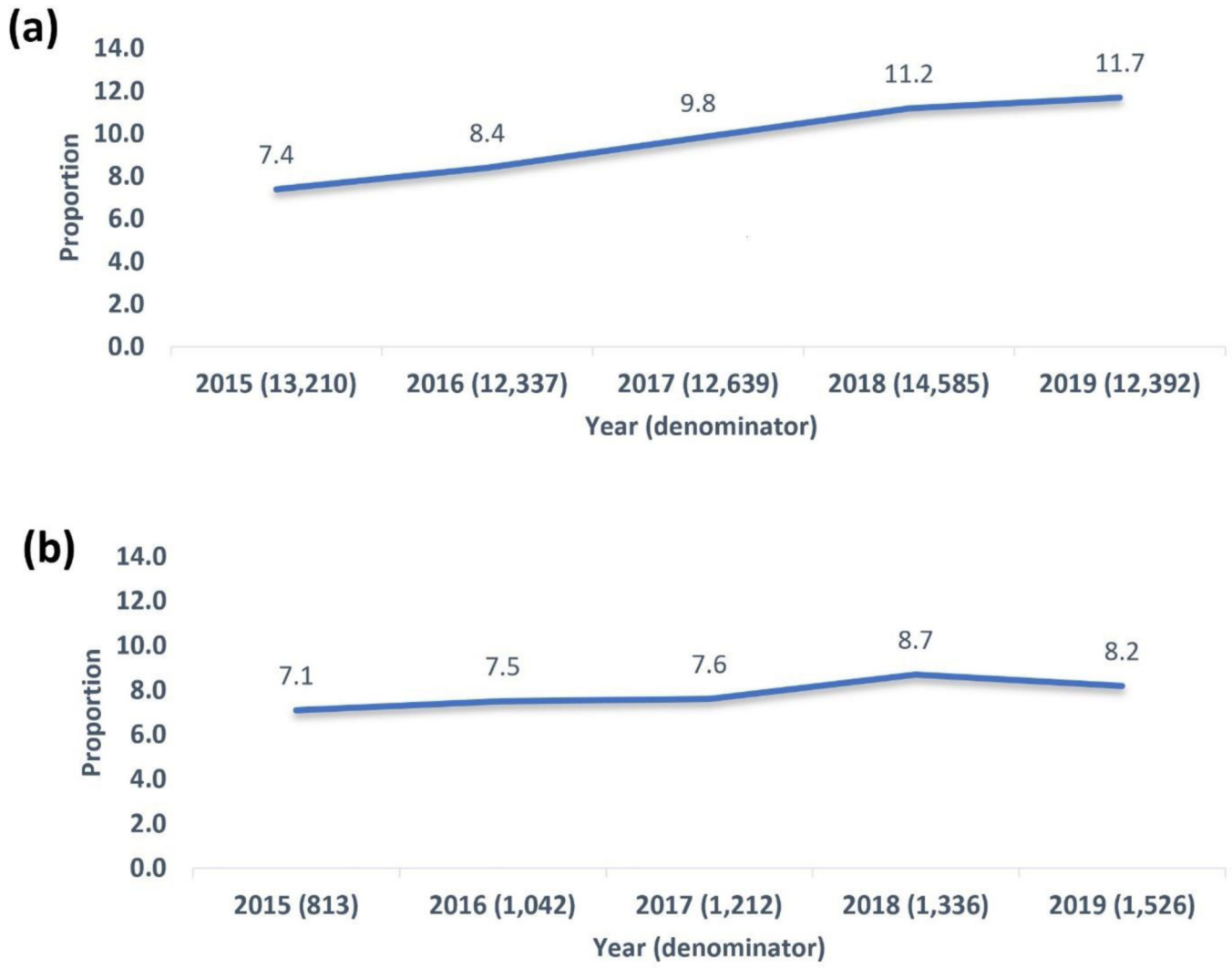

Figure 4a-b.

Trends in the proportion of episodes of men diagnosed with urethritis who had ≥1 symptomatic* follow-up visits† from 2015–2019 by (a) treatment with azithromycin regimen (n=65,601) and (b) treatment with doxycycline non-azithromycin regimen (n=5,957), STD Surveillance Network

*includes dysuria and/or discharge; †within 45 days of initial presentation.

Note: Poisson model was also used to assess statistical significance in trends in the proportion over time estimating the annual percent change from the regression coefficient for the year of the episode. (a) APC, 12.6%; 95% CI, 8.6–16.7; (b) APC, 4.3%; 95% CI, −0.3–9.2

Table 1.

Characteristics of unique male patients and urethritis episodes, 2015– 2019, STD Surveillance Network

	Unique men n=67,546		Episodes n=99,897	
Jurisdiction	n	%	n	%
Baltimore, MD	5,180	7.6	7,175	7.2
Multnomah, OR	1,967	2.9	2,560	2.6
Minneapolis, MN	7,973	11.8	11,986	12.0
New York City, NY	36,481	54.1	55,736	55.8
Philadelphia, PA	6,988	10.4	9,022	9.0
San Francisco, CA	6,299	9.3	9,925	9.9
Seattle, WA	2,658	3.9	3,493	3.5
Age (in years)				
≤19	2,125	3.2	2,562	2.6
20 – 24	9,833	14.6	13,186	13.2
25 – 34	30,030	44.5	45,400	45.5
35–44	13,402	19.8	20,288	20.3
45+	12,151	18.0	18,455	18.5
Missing	5	<0.1	6	<0.1
Race/ethnicity				
NH White	16,378	24.3	22,773	22.9
NH Black	31,263	46.3	47,823	47.6
Hispanic	12,681	18.8	18,929	18.9
NH Asian	2,519	3.7	3,341	3.3
NH Other*	4,027	6.0	6,260	6.3
Missing	678	1.0	771	0.8
Sexual Behavior				
MSW	40,862	60.5	57,180	57.2
MSM	25,074	37.1	41,062	41.1
M_{unk}	1,610	2.4	1,655	1.7
Living with HIV	4,957	7.3	8,690	8.7
No of episodes				
1	50,192	74.3	50,192	50.2
2	10,166	15.1	20,332	20.4
3+	7,188	10.6	29,373	29.4

* includes multi-race, other race, American Indian/Alaskan Native

MD= Maryland; OR = Oregon, MN = Minnesota; NY = New York; PA = Pennsylvania; CA= California; WA = Washington; NH = Non-Hispanic; MSM= gay, bisexual, and other men who have sex with men; MSW = men who have sex with women only; M_{unk}= men with unknown gender of sexual partners