Etiological Surveillance of Male Urethritis Syndrome in South Africa: 2019 to 2020

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Background: In South Africa, male urethritis syndrome (MUS) is the most common sexually transmitted infection (STI) syndrome in men. We determined the distribution of STI etiologies and the susceptibility profiles of *Neisseria gonorrhoeae* isolates from men presenting with MUS to 3 sentinel surveillance health care facilities. Secondary objectives were to determine the seroprevalence of coinfections (HIV, syphilis, herpes simplex virus 2).

Methods: Consecutive, consenting men with symptomatic urethral discharge were enrolled between January 1, 2019, and December 31, 2020. Genital discharge swab and blood specimens were collected and transported to a central STI reference laboratory in Johannesburg, South Africa.

Results: Among 769 men enrolled, *N. gonorrhoeae* was the commonest cause of MUS (674 [87.8%]; 95% confidence interval [CI], 85.2%–89.9%), followed by *Chlamydia trachomatis* (161 [21.0%]; 95% CI, 18.2%–24.0%). Of 542 cultivable *N. gonorrhoeae* isolates, all were susceptible to ceftriaxone (modal minimum inhibitory concentration, 0.004 mg/L) and azithromycin (modal minimum inhibitory concentration, 0.128 mg/L). Seroprevalence rates of HIV, syphilis, and HSV-2 were 21.4% (95% CI, 18.5%–24.5%), 2.3%, and 50.1%, respectively. Condom use at last sexual encounter was reported by only 7%, less than 50% had been medically circumcised, and only 66.7% (58 of 87) who self-reported an HIV-positive status were adherent on antiretroviral drugs.

Conclusions: *Neisseria gonorrhoeae* and *C. trachomatis* were the predominant causes of MUS. Currently recommended dual ceftriaxone and azithromycin therapy are appropriate for MUS syndromic management; however, surveillance must be maintained to timeously detect emerging and increasing gonococcal resistance. Clinic-based interventions must be intensified in men seeing sexual health care to reduce the community transmission and burden of STI and HIV.

In South Africa, sexually transmitted infections (STIs) are managed principally at primary health care centers (PHCs) using standard syndromic management guidelines.[1] Syndromic management of STIs involves treatment of the most common causes of a particular syndrome. It is deemed to be a pragmatic and cost-effective strategy where resources or infrastructure for universal etiological testing are unavailable or inaccessible. Male urethritis syndrome (MUS) is the most common STI syndrome in men presenting to primary PHCs in South Africa.[2]

The World Health Organization (WHO) has stated that strengthening of national STI surveillance is integral to syndromic management.[3] The Centre for HIV & STI at the National Institute for Communicable Diseases (NICD) conducts sentinel etiological surveillance of STI syndromes to validate or revise existing treatment algorithms. An important component of this surveillance is the monitoring of *Neisseria gonorrhoeae* antimicrobial susceptibility profiles. *Neisseria gonorrhoeae*, the causative agent of gonorrhea, is the commonest cause of male urethritis in South Africa.[4] The organism evolves rapidly and has a propensity to acquire resistance to all first-line antimicrobials used in treatment.[5] Since 2015, the recommended treatment for gonorrhea in national syndromic guidelines has been a combination of intramuscular single-dose ceftriaxone 250 mg and oral azithromycin 1 g.[1] This dual antimicrobial therapy was recommended by the WHO to curb the emergence of resistance to ceftriaxone, the mainstay of gonorrhea treatment. Azithromycin also covers *Chlamydia trachomatis*, which is the second most common etiology and prevalent in approximately 20% of cases.[4] Etiological and antimicrobial resistance testing is recommended for persistent STI syndromes and symptoms that fail to resolve within 7 days of standard syndromic therapy. Ceftriaxone-resistant gonorrhea is a category 3 Notifiable Medical Condition in South Africa, and laboratories are required to notify the National Department of Health and the NICD within 7 days of culture of a resistant isolate.[6]

Before 2019, the NICD conducted sentinel STI etiological surveillance annually in Gauteng (GP), and periodically at high volume STI clinics in other provinces. Since 2019, surveillance has been conducted at 3 fixed sentinel sites in key provinces: GP, Western Cape (WC), and KwaZulu Natal (KZN). We describe the results of STI surveillance in adult men presenting with genital discharge to these facilities in 2019 to 2020. The primary objective of surveillance was to determine the etiologies of MUS and the susceptibility profiles of *N. gonorrhoeae* isolates. Secondary objective was to determine STI coinfections (i.e., HIV, syphilis, herpes simplex virus 2) in men presenting with symptomatic urethral discharge.

MATERIALS AND METHODS

Design

We conducted an observational cross-sectional study of the prevalence of relative STI etiologies.

Setting

Three primary care facilities that are high-volume STI sentinel sites were as follows: Alexandra Health Centre (GP), Spencer Road Clinic (WC), and Prince Cyril Zulu Communicable Disease

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Acknowledgments: The authors thank Ms Valentia Kekana and Mr Alex Vezi (Gauteng), Ms Nokuthula Nzuza (KwaZulu Natal), and Ms Zukiswa Mithani (Western Cape) for participant enrollment, questionnaire administration, and specimen collection at sentinel surveillance sites. In addition, the authors wish to acknowledge Ms Lindy Gumede for *Neisseria gonorrhoeae* culture and antimicrobial susceptibility testing, and Ms Thabitha Mathega for data entry and quality checks.

Conflict of Interest and Source of Funding: All authors have no conflicts of interest to declare. Funding for this work was obtained from the operational cost center of the Centre for HIV & STI at the National Institute for Communicable Diseases, Johannesburg, South Africa.

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Received for publication January 25, 2022, and accepted May 6, 2022.
DOI: 10.1097/OLQ.0000000000001647

Centre (KZN). Surveillance has been conducted annually at Alexandra Health Centre since 2008. Surveillance was commenced at Spencer Road Clinic in May 2019 and at Prince Cyril Zulu CDC in April 2020.

The MUS sample size was calculated based on an estimated *N. gonorrhoeae* prevalence of 75%: using a confidence level of 95% with 5% margin of error, 288 participants were required from each site. In addition, to obtain at least 100 viable gonococcal isolates from each PHC, it was estimated that a minimum of 150 men with MUS would need to be enrolled per site for gonococcal culture and antimicrobial susceptibility testing procedures.

Participants

Consecutive consenting men presenting with any visible urethral discharge ± dysuria to the selected PHCs between January 1, 2019 and December 31, 2020, were enrolled in the surveillance. Inclusion criteria included participants 18 years and older with a new episode of clinically confirmed MUS. Following eligibility ascertainment and informed consent procedures, a nurse-administered questionnaire (paper-based or electronic) was used to document demographic and clinical information. Each participant was assigned a unique survey ID number that was not linked to any personal identifiers.

Specimen Collection

Surveillance nurses collected swab specimens of urethral discharge using the Eswab collection system (Copan Italia SpA, Brescia, Italy). Eswab specimens from GP were inoculated directly on New York City agar (Diagnostic Media Products, National Health Laboratory Service). Agar plates were then placed in a holding candle jar, before same-day transfer, together with the Eswab specimens, to the STI reference laboratory at the Centre for HIV & STI, NICD, in Johannesburg, South Africa. Urethral Eswab specimens from other provinces were transported directly to the STI reference laboratory.

In addition, a 10-mL venous blood specimen was collected from each participant for serological testing. All swab and blood specimens were transported on ice to the STI reference laboratory and arrived, on average, within 24 to 48 hours of collection.

Laboratory Testing

N. gonorrhoeae Culture and Antimicrobial Susceptibility Testing

Eswab specimens from KZN and WC sites were vortexed, and a 100-µL volume of liquid Amies medium from each plastic tube was transferred onto New York City agar using a sterile pipette. All inoculated agar plates were incubated at 35°C to 37°C in 5% to 10% CO_2 and examined daily for growth up to a total of 72 hours. Suspected *N. gonorrhoeae* colonies were definitively identified using a biochemical test (oxidase) and a specific slide coagglutination immunological assay: the Phadebact Monoclonal GC test (MKL Diagnostics AB, Kung HansVag, Sollentuna, Sweden). Antimicrobial susceptibility testing for cefixime and ceftriaxone was performed using E-test (bioMérieux, Marcy-l'Étoile, France), whereas agar dilution batch testing was done for azithromycin minimum inhibitory concentration (MIC) determination, according to established standard operating protocols based on Clinical and Laboratory Standards Institute methodology. Antimicrobial MICs were interpreted according to the criteria recommended by the European Committee on Antimicrobial Susceptibility Testing.[7] A panel of WHO reference strains of *N. gonorrhoeae*, with known MICs for each antimicrobial, was included in every batch of clinical isolates tested for the purpose of quality control.[8]

Molecular Testing

DNA was extracted from swab specimens using 1 of 2 automated DNA extractors, that is, MagNA Pure Compact system (Roche, Basel, Switzerland) or QIAcube HT instrument (Qiagen, Hilden, Germany). DNA extracts were tested using a validated in-house real-time multiplex polymerase chain reaction (PCR) assay on the Rotor-Gene Q real-time platform (Qiagen) for discharge-causing STI pathogens: *N. gonorrhoeae*, *C. trachomatis*, *Trichomonas vaginalis*, and *Mycoplasma genitalium*.

Serology

Serum specimens were screened for HIV using the Architect Syphilis TP kit (Abbott, Wiesbaden, Germany) and for HSV-2 infection using the Focus HerpeSelect 2 ELISA IgG assay (Focus Diagnostics, Cypress, CA). Syphilis coinfection was detected by screening with the Architect Syphilis TP kit (Abbott). Specimens giving positive specific treponemal results were reflexively tested using a rapid plasma reagin (RPR) assay (Immutrep; Omega Diagnostics Ltd, Alva, United Kingdom).

Data Analysis

Data from clinical questionnaires and Excel spreadsheets of laboratory data were exported into Stata 16 (Stata Corporation, College Station, TX) for analysis. The enrolled participants were described using frequencies and proportions for categorical data, and medians and interquartile ranges (IQRs) for continuous variables. The relative prevalence of the different STI pathogens and seroprevalence of HIV, HSV-2, and RPR were determined as proportions with 95% confidence intervals (CIs) around them. χ^2 Tests were used to identify associations between various exposure variables and site of enrollment. Analysis of antimicrobial susceptibility trends in *N. gonorrhoeae* involved determination of MIC range, modal MIC, MIC_{50} (the minimum concentration needed to inhibit 50% of isolates), and MIC_{90} (the minimum concentration needed to inhibit 90% of isolates). We included data obtained for 2 years of surveillance to have an adequate sample size for analysis.

RESULTS

Patient Demographic and Clinical Characteristics

A total of 769 men were enrolled during the surveillance period: 345 (44.9%) from GP, 233 (30.3%) from WC, and 191 (24.8%) from KZN provinces (Table 1). The median age of participants was 30 years (IQR, 25–36 years). A smaller proportion of participants in WC were younger than 25 years relative to the other sites. A majority were of Black African ethnicity and of self-reported heterosexual orientation. With respect to sexual behaviors, the median age at sexual debut was 17 years (IQR, 15–18 years), and less than 10% self-reported condom use at last sexual encounter. Condom use was significantly lower in KZN and WC sites compared with GP. Approximately one-fifth of participants overall had been diagnosed with an STI syndrome within the preceding 12-month period; and this proportion was higher in the WC at 36.1%. The median number of sex partners in the preceding 3-month period was reported to be 2 (range, 1–6). Overall, 58.3% reported having multiple sexual partners in the past 3 months, and a similar proportion stated that their most recent sexual encounter was with a nonregular partner (this proportion was higher at the WC site). A greater proportion of participants in GP reported having sex with a partner in another province (33%) or country (29%) in the preceding 3-month period. Most of these sexual partners outside the province of enrollment were based in KZN (42.9%) and the Eastern Cape (24.3%), and a majority of partners outside the country were resident in neighboring

TABLE 1. Demographic and Behavioral Characteristics of Participants With MUS (N = 769)

Variable	All (N = 769)	GP	KZN	WC	*P*
n (%)		345 (44.9)	191 (24.8)	233 (30.3)	
Current age, median (IQR), y	30 (19–36)	28 (25–32)	30 (25–35)	33 (27–40)	<0.001
Age <25 y, n (%)	139 (18.1)	78 (22.6)	31 (16.2)	30 (12.9)	0.009
Black Africans, n (%)	760 (98.8)	345 (100)	191 (100)	224 (96.1)	<0.001
Age at first sex, median (IQR), y	17 (15–18)	17 (15–18)	17 (16–19)	16 (15–18)	<0.001
Heterosexual orientation, n (%)	765 (99.5)	343 (99.4)	190 (99.5)	232 (99.6)	0.970
Condom use at most recent sexual encounter, n (%)	52 (6.8)	37 (10.7)	3 (1.6)	12 (5.2)	<0.001
Casual sexual partner (past 3 mo), n (%)	451 (58.6)	171 (49.6)	105 (55.0)	175 (75.1)	<0.001
Sex outside province (past 3 mo), n (%)	177 (23.0)	137 (39.7)	4 (2.1)	36 (15.5)	<0.001
Sex outside country (past 3 mo), n (%)	100 (13.0)	96 (27.8)	0 (0.0)	4 (1.7)	<0.001
STI syndrome diagnosed in the past 12 mo, n (%)	152 (19.8)	17 (4.9)	51 (26.7)	84 (36.1)	<0.001
Treated for MUS symptoms with no success (past 3 mo), n (%)	27 (3.5)	3 (0.9)	6 (3.1)	18 (7.7)	<0.001
Know their HIV status, n (%)	675 (87.8)	262 (75.9)	182 (95.3)	231 (99.1)	<0.001
Self-reported being HIV positive*, n (%)	87 (12.9)	19 (7.2)	27 (14.8)	41 (17.8)	0.002
Taken ARVs in the past 3 d†, n (%)	58 (66.7)	15 (79.0)	26 (96.3)	17 (41.5)	<0.001
Males ever circumcised, n (%)	528 (68.7)	219 (63.5)	108 (56.5)	201 (86.3)	<0.001
Males ever circumcised medically‡, n (%)	241 (45.6)	126 (57.5)	86 (79.6)	29 (14.4)	<0.001

*Among those who reported knowing HIV status.
†Among those who self-reported being HIV positive.
‡Among those circumcised.

Zimbabwe (47%). In total, 675 (87.8%) participants reported knowledge of their HIV status; of these 87 (12.9%) self-reported being HIV positive. Only 67% of those who said they were HIV infected had taken antiretroviral drugs (ARVs) in the past 3 days. Overall, 68.7% of males were circumcised, of whom only 45.6% had been medically circumcised. There was no protective association between the prevalence of any STI pathogens and circumcision status, that is, 227 of 241 (94.2%) in uncircumcised versus 510 of 428 (96.6%) in circumcised ($P = 0.122$). Similarly, there was no association between any STI prevalence and circumcision method (i.e., medical vs. traditional circumcision; data not shown). Among 514 circumcised men who had an HIV result, there was no difference in the crude odds of HIV positivity between those who were medically and traditionally circumcised (odds ratio, 0.90; 95% CI, 0.59–1.38; $P = 0.637$).

Laboratory Results

STI Syndrome Etiologies and *N. gonorrhoeae* Antimicrobial Resistance Profiles

Among 768 participants presenting with MUS who had valid STI etiology results, *N. gonorrhoeae* was the commonest cause (674 [87.6%]; 95% CI, 85.2%–89.9%), followed by *C. trachomatis* (161 [21.0%]; 95% CI, 18.2%–24.0%; Fig. 1). The majority of men (608 [79.2%]; 95% CI, 76.1%–81.9%) had infections caused by single agents. *Trichomonas vaginalis* and *M. genitalium* together accounted for less than 5% of MUS. Multiple pathogens were detected in approximately 16.8% (129; 95% CI, 14.3%–19.6%): a majority of these mixed infections (123 [95.3%]) were caused by *N. gonorrhoeae* in combination with other STI pathogens, mostly *C. trachomatis* (101 [78.3%]). An STI pathogen was detected in approximately 96.0% of specimens (737; 95% CI, 94.3%–97.1%); only 4.0% of specimens (32; 95% CI, 2.9%–5.7%) had no identifiable STI etiology.

In total, 542 of 674 specimens that tested positive for *N. gonorrhoeae* by real-time multiplex PCR (80.4%) were also culture positive. There were no culture-positive specimens that tested PCR negative for *N. gonorrhoeae*. Culture isolation rates were affected by specimen transport method and transit time to laboratory from the different sites: 95% to 100% from the GP site versus 60% to 85% from the KZN and WC sites. All gonococcal culture isolates were sensitive to ceftriaxone (ceftriaxone MIC_{50}, 0.004 mg/L; MIC_{90}, 0.004 mg/L; modal MIC, 0.004 mg/L; Table 2). The modal cefixime MIC was <0.016 mg/L; only 1 isolate from WC had a cefixime MIC that was at the resistance breakpoint of 0.25 mg/L. The ceftriaxone and azithromycin MICs for this cefixime-resistant isolate were 0.064 and 0.25 mg/L, respectively. Overall azithromycin MICs ranged from 0.032 to 1 mg/L, with a modal MIC of 0.128 mg/L. No isolates had azithromycin MICs that were above the epidemiological cutoff value of 1 mg/L.

Serological Results

HIV coinfection rate among all participants was 21.4% (161 of 752; 95% CI, 18.5%–24.5%), and syphilis serology (RPR) was positive in 17 of 753 (2.7%; 95% CI, 13.2%–35.9%). The relative prevalence of both HIV and syphilis coinfection was higher in KZN at 31.5% (95% CI, 24.9%–38.8%) and 4.9% (95% CI, 2.2%–9.0%) than at sites in the other 2 provinces. Overall HSV-2 seropositivity was 50.1% (380 of 758; 95% CI, 46.5%–53.8%) and ranged from 40.1% in GP to 59.8% in WC.

DISCUSSION

N. gonorrhoeae was the predominant cause of MUS. Based on our data, syndromic management for MUS in the South African public health sector should include cover for the 2 leading causes, *N. gonorrhoeae* and *C. trachomatis*. Extensively drug-resistant (XDR) *N. gonorrhoeae* (resistant to ceftriaxone and azithromycin) was not detected through surveillance. The modal MICs and MIC_{90} for the extended-spectrum cephalosporins tested showed that a majority of isolates remain highly susceptible to both ceftriaxone and cefixime. The MIC_{90} for azithromycin remained 3 dilutions below the resistance breakpoint of 2 mg/L. This suggests that the currently recommended first-line dual regimen of ceftriaxone-azithromycin is still appropriate for the empiric treatment of gonorrhea in South Africa. One isolate exhibited resistance to cefixime at our WP site; however, it was susceptible to standard first-line therapy for gonorrhea, and further information on clinical response was unavailable. We were not alerted by the surveillance nurse to any returning patients with refractory or persistent symptoms that failed to respond to the recommended dual treatment regimen. Most men reported multiple sexual partners and recent sex with casual partners. It is hypothesized that

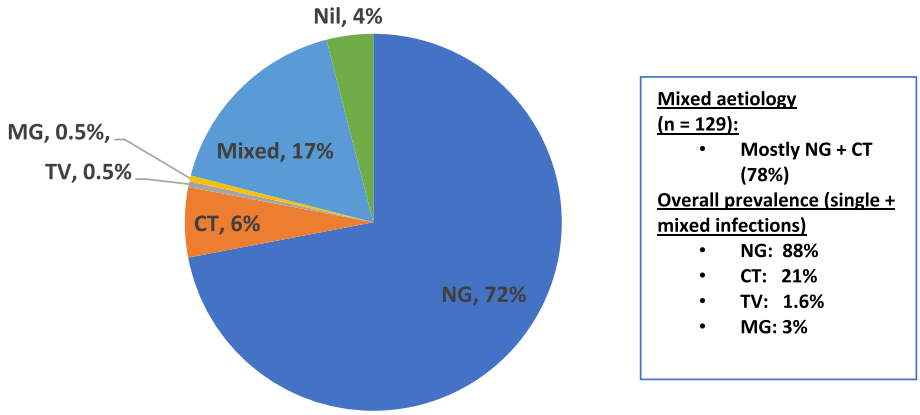

Figure 1. Relative prevalence of STI pathogens in MUS (N = 768). CT, *Chlamydia trachomatis*; MG, *Mycoplasma genitalium*; NG, *Neisseria gonorrhoeae*; TV, *Trichomonas vaginalis*. Figure 1 can be viewed online in color at www.stdjournal.com.

sexual network connectivity with high partner concurrency and partner exchange sustains a high prevalence of *N. gonorrhoeae*, with risk of antimicrobial resistance due to reinfection and selection pressure from antibiotics used in recent treatment.[9] This emphasizes the importance of continued gonococcal antimicrobial resistance surveillance in this population. Promotion of consistent condom use with ready access to free supply is an essential intervention.

We have previously investigated the demographic and risk factors associated with reduced susceptibility to first-line antigonorrhea agents among men with symptomatic urethritis presenting to our sentinel facilities.[10] Only recent sex outside the country was a risk for infection with a decreased susceptible or resistant gonococcal isolate. Our data on sex outside the province and country of enrollment reflect the high population mobility in GP province, which is the economic hub of South Africa, attracting migrant workers from other provinces and neighboring sub-Saharan African countries. There has been only 1 published report of gonococcal extended-spectrum cephalosporin resistance in South Africa, of 2 men who have sex with men (MSM) presenting with cefixime treatment failure.[11] Both men had possible links to overseas sexual networks in North America and Europe. Cases of the ceftriaxone-resistant FC428 strain have been linked to sexual networks in Southeast Asia and Europe, and underline the association between cross-border travel and the global dissemination of XDR gonorrhea.[12–14] The vast majority of our participants self-reported heterosexual orientation. At a men's sexual health center in Cape Town catering for MSM and transgender women, a majority of STIs were asymptomatic and at extragenital (rectal/pharyngeal) sites.[15] There is a risk of evolution of *N. gonorrhoeae* antimicrobial resistance at the pharyngeal site, and it is important to confirm eradication of infection at this site by performing a test of cure after treatment.[16] To ascertain the true prevalence of XDR gonorrhea in South Africa, it would be therefore essential to extend routine STI syndrome etiological and antimicrobial resistance surveillance to the screening of high-risk groups, such as MSM.

National treatment guidelines for gonorrhea in the United States, the United Kingdom, and Europe have moved away from the use of dual therapy in favor of high-dose (500 mg–1 g) intramuscular single-agent ceftriaxone.[17,18] One reason is the evidence of increasing azithromycin MICs in *N. gonorrhoeae*, as well as the clonal dissemination of high-level azithromycin-resistant gonococcal strains.[19,20] Another is the risk of selection of azithromycin resistance in other STI pathogens (*M. genitalium*) as well as organisms in the respiratory and gut microbiomes, such as *Streptococcus pneumoniae* and *Campylobacter* species, with recent use of azithromycin.[17,21] Because of its relatively long half-life, organisms are exposed to prolonged subinhibitory concentrations even after a single dose of azithromycin, which can select for stepwise point mutations in 23S rRNA resulting in macrolide resistance.[22] Unlike high-income countries with facilities for etiological screening and pathogen-directed therapy, South Africa uses syndromic management to cover for multiple etiologies in symptomatic persons. It is essential, therefore, that syndromic management for MUS is also able to adequately treat *C. trachomatis*. Currently, macrolide resistance in *M. genitalium* is uncommon among STI clinic attendees in South Africa (unpublished data), and the azithromycin susceptibility profiles observed in contemporary *N. gonorrhoeae* isolates do not yet warrant a change in syndromic management guidelines.

A male medical circumcision program has been implemented by the South African National Department of Health as an HIV prevention strategy since 2010. Medical circumcision was shown to have a protective association with HSV-2, HIV, hepatitis B, and *M. genitalium* infection among men in KZN.[23] This protective effect against HIV and HSV-2 also extended to female partners.[23] The circumcision status of men in our study was less than 70% and significantly lower at the KZN site. Although the prevalence of circumcision was highest in the WP, the majority had been traditionally circumcised. Traditional circumcision may involve only partial removal of the foreskin, and therefore, the impact on STI and HIV acquisition may be lower than with medical circumcision.

TABLE 2. *Neisseria gonorrhoeae* MICs* to First-Line Antimicrobials

Antimicrobial	MIC Range	MIC_{50}	MIC_{90}	Modal MIC
Ceftriaxone (n = 542)	<0.002–0.064	0.004	0.004	0.004
Cefixime (n = 542)	<0.016–0.25	<0.016	<0.016	<0.016
Azithromycin (n = 533)†	0.032–1	0.128	0.25	0.128

*MIC indicates minimum inhibitory concentration in mg/L.
†Nine isolates were nonviable on culture for azithromycin agar dilution testing.

However, a recent study among adult males in a mining town in South Africa revealed a strong protective effect against symptomatic urethritis in both medically and traditionally circumcised men, even after controlling for potential confounders such as employment status and condom use.[24] We did not find an association between STI or HIV positivity and circumcision method among our participants with symptomatic urethral discharge, as these were high-risk individuals for both HIV and STIs.

The strengths of our study included a large sample size of men with urethritis for whom matching demographic, clinical, and laboratory data were available. Limitations included the fact that a majority of participants were recruited at the surveillance site in the most populous province of the country (GP), thus limiting the generalizability of findings to other regions. Although our 3 sentinel surveillance sites are located in diverse geographical locations and close to transport links, all are urban clinics in large commercial cities and not representative of urban and rural populations across the entire country. In addition, many of the exposure variables were self-reported by participants, and social desirability bias may have influenced some of the responses. We found that less than three-quarters of men who self-reported a positive HIV status were adherent on ARVs. This highlights a significant gap in the integration of sexual health services in men. The high prevalence of STI coinfections such as HIV and syphilis, particularly at the KZN site, underscores the importance of linkage to universal HIV and syphilis screening and treatment among males presenting with symptomatic urethritis. HIV counseling and testing is a key component of the total care package for patients presenting with STI syndromes who report a negative or unknown HIV status; however, this needs to be combined with adequate ARV adherence counseling and support services. Syphilis serological screening is not routinely performed for STI clinic attendees: currently validated tests are laboratory-based assays that require return to clinic for follow-up of results. Commercially available rapid point-of-care tests are largely treponemal assays, which may have suboptimal sensitivity when performed by health care workers using capillary fingerprick whole blood. These need to be evaluated and validated in our STI clinic attendees, for incorporation into onsite syphilis screening algorithms. Collectively, these interventions will contribute to a reduction in transmission to partners and the overall community burden of STI and HIV.

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