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Sexually transmitted infections surveillance among a high-risk men who have sex with men (MSM) cohort in Johannesburg, South Africa, 2023

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Summary

In South Africa, screening for sexually transmitted infections (STIs) among men who have sex with men (MSM) is not routinely available in the public sector, and current STI management guidelines do not include algorithms for screening or treatment of extragenital infections. This report summarises the first year of comprehensive STI surveillance among high-risk members of this key population from a single NGO partner site in Johannesburg. Participants were stratified based on the presence or absence of urethral discharge at enrolment. Among the 131 participants recruited, the prevalence of extragenital (pharyngeal and/or rectal) STIs was 35% and 41% among MSM with and without urethral discharge, respectively. Overall, 17.6% of participants were reactive for non-treponemal rapid plasma reagin (RPR) and approximately a quarter (24.4%) were reactive for HIV. *Neisseria gonorrhoeae* antimicrobial susceptibility testing revealed all isolates were susceptible to the third-generation cephalosporins, ceftriaxone, and cefixime, whilst one urethral isolate was resistant to azithromycin. These findings highlight the importance of continued and expanded aetiological STI surveillance, with a specific focus on *N. gonorrhoeae* antimicrobial susceptibility testing, amongst all high-risk members of this key population, regardless of symptoms. Furthermore, national STI management guidelines should be updated to include aetiological screening and pathogen-directed treatment recommendations for extragenital infections among MSM.

Introduction

Men who have sex with men (MSM) and transgender women (TGW) are considered key populations (KP) because they are at increased risk of acquiring HIV and sexually transmitted infections (STIs). This is in part due to biological factors, engagement in high-risk sexual practices, and structural barriers to accessing healthcare services. UNAIDS recommends that the MSM population size estimates should be at least 1% of the adult male general population.[1] Thus, based on the 2022 South African national census results[2], there should be at least an estimated 218,000 MSM aged 15 and older. A recent national survey revealed that the majority of MSM, 86%[3], utilise the public healthcare system in which STIs are managed syndromically with a focus on urogenital symptoms only.[4] However, the anatomical sites of infection among MSM include the oro-pharynx and rectum, collectively referred to as extragenital sites, with infections at these sites being largely asymptomatic.

The bacterium *Neisseria gonorrhoeae* is the most common cause of male urethritis syndrome (MUS) and the second most common bacterial cause of vaginal discharge syndrome (VDS) in South Africa.[5,6] Antimicrobial resistance (AMR) in *N.gonorrhoeae* is a major public health concern due to the organism's ability to rapidly acquire resistance to all previously recommended antimicrobials for the treatment of gonorrhoea. Globally, reduced susceptibility and antimicrobial resistance to the current regimens, namely the extended-spectrum cephalosporin (ESC), ceftriaxone, and azithromycin, is increasing among gonococci, thereby limiting available treatment options. Importantly, pharyngeal gonorrhoea is harder to eradicate than urogenital or anorectal infections and has been associated with the development of resistance.[7] In South Africa, studies investigating the STI prevalence among MSM are limited, and antimicrobial resistance surveillance in this population is lacking.

The overall aim of this surveillance study was to determine the burden of asymptomatic extragenital STIs and examine the aetiologies of symptomatic male urethritis. In addition, we sought to monitor for *N. gonorrhoeae* resistance in culture-positive isolates as well as detect other emerging STI pathogens in high-risk MSM from Johannesburg.

Methods

Study design and setting

A cross-sectional study of STI aetiologies among MSM attending the Engage Men's Health (EMH) Clinic in Melville, Johannesburg, was conducted from 11 April to 15 September 2023. Eligible participants were: i) adult (≥ 18 years) men or transgender women (i.e., a patient registered as male at birth); ii) who reported sex (oral or anal) with another man in the past 3 months regardless of sex with women; iii) who were given information on the study by an NICD-appointed professional nurse; and iv) provided written consent to participate, including the long-term storage of samples for future research. MSM presenting with urethral discharge (symptomatic) were enrolled regardless of other risk factors in the past 3 months. In contrast, MSM without urethral discharge at enrolment (asymptomatic for urethritis) were required to self-report one or more risk factors in the past 3 months. The risk factors assessed for inclusion are shown in Table 1.

Data collection procedures

Following written informed consent procedures, participants completed a nurse-administered electronic questionnaire on demographic, behavioural, and clinical characteristics.

Sample collection

Oropharyngeal and rectal ESwab® (Copan Italia SpA, Brescia, Italy) specimens were collected from all participants. Endo-urethral ESwab® specimens were only collected from participants presenting with visible urethral discharge. In addition, a 10ml venous blood specimen was collected from each participant for serological testing.

Laboratory procedures

All laboratory tests were performed at the Sexually Transmitted Infections (STI) reference laboratory, Centre for HIV and STIs, National Institute for Communicable Diseases/NHLS. The molecular detection of common STI aetiological agents, namely *Neisseria gonorrheae*, *Chlamydia trachomatis*, *Trichomonas vaginalis,* and *Mycoplasma genitlaium*, in specimens from all anatomical sites was performed using a previously validated in-house real-time multiplex PCR assay. All positive results were confirmed with commercial kit assays. Eswabs® were also subjected to *N. gonorrhoeae* culture and antimicrobial susceptibility testing (AST) for cefixime, ceftriaxone, and azithromycin using E-tests™ (bioMérieux, Marcy-l'Étoile, France). Serological assays for HIV (HIV Ag/Ab), Hepatitis B surface antigen (HBsAg Qualitative), and specific treponemal antibodies (syphilis TP) were performed on the Architect system (Abbott, Wiesbaden, Germany). Specimens reactive for specific treponemal antibodies were reflexively tested using the non-treponemal rapid plasma reagin (RPR) assay (Immutrep®, Omega Diagnostics Ltd, Alva, UK). In general, active syphilis in MSM is defined as an RPR titre > 1:8.[8] However, treatment for syphilis in primary care settings in South Africa is provided to all RPR seropositive patients upon baseline screening, regardless of RPR titre.[4]

Data analyses

REDCap electronic questionnaire data and excel-based laboratory data were exported, merged, and analysed using Stata SE 18.0 (Stata Corporation, College Texas, USA). Descriptive statistics were used to describe enrolled men and determine the prevalence of genital and extragenital STIs, comparing those with or without urethritis. Chi-squared tests and Wilcoxon rank-sum tests were used to determine if there were any statistically significant differences between those with or without urethritis with respect to demographic, clinical, and behavioural characteristics. *Neisseria gonorrhoeae* antimicrobial susceptibility analyses involved determining MIC range, MIC_{50} and MIC_{90} (the minimum concentrations required to inhibit 50% and 90% of isolates, respectively).

Results

A total of 131 MSM participated in the 2023 survey, of which 48 (37%) presented with urethral discharge at enrolment. Demographic and behavioural characteristics are presented in Table 1.

The median age of participants was 29 years (IQR 26-33 years). The majority were of black African ethnicity, self-identified as male (99%), and reported exclusive sex with men (81.7%) in the preceding three-month period. Self-reported knowledge of HIV status was high, with 84.4% correctly self-reporting as HIV seropositive, using the laboratory test result as a reference. A quarter of participants self-reported engaging in sex with partners residing in another South African province (Western Cape, KwaZulu-Natal, and Mpumalanga), whilst approximately one in seven (13.8%) reported international sexual contacts (predominantly other African countries, Europe, and a single report of sex with a partner from Southeast Asia). Approximately one in five MSM (22.2%) self-reported history of an STI, namely urethral discharge, genital ulcers, and/or genital warts, in the past six months. Stratification based on symptoms revealed that MSM with urethral discharge were more likely to identify as bisexual/pansexual and less likely to engage in 1) condomless receptive anal sex with a casual partner; 2) receptive fellatio, and 3) receptive oro-anal sex (passive rimming) in the preceding 3 months (Table 1).

Overall, the detection of STI pathogens at extra genital anatomical sites (pharynx and/or rectum) was common at 39% (51/131); that is, 41% (34/83) among MSM without urethral discharge and 35% (17/48) among participants presenting with urethral discharge at enrolment (Table 2). The overall prevalence of pharyngeal STI infections was below 2.5% (Figure 1). *Neisseria gonorrhoeae* was the predominant rectal pathogen in both subgroups, whilst anorectal infections with *C. trachomatis* (12.7% vs 4.3%) and *M. genitalium* (15.2% vs 4.3%) were higher among MSM without urethral discharge compared to those with visible urethral symptoms, although this did not reach significance (Table 2). Most STIs at the rectal site were caused by a single agent, with co-infections with multiple pathogens accounting for only 1/16 (6.3%) and 5/34 (14.7%) of anorectal STIs in MSM with and without urethral discharge, respectively (Figure 1).

Table 1. Demographic and sexual behavioural characteristics of men who have sex with men (MSM) enroled into the 2023 sexually transmitted infections (STI) surveillance study at the Engage Men's Health (EMH) Clinic in Melville, Johannesburg, South Africa (SA).

	All eligible patients (N=131)	Patients without urethral discharge (N=83)	Patients with urethral discharge (N=48)	P
Age (median, IQR)	29 (26-33)	29 (26-34)	29 (26-32)	0.29
Ethnicity				
African	107 (81.7)	63 (75.9)	44 (91.6)	
White	16 (12.2)	14 (16.9)	2 (4.2)	0.09
Coloured	7 (5.3)	5 (6.0)	2 (4.2)	
Indian	1 (0.8)	1 (1.2)	0	1.00
Gender Identity (n, %)				
Male	130 (99.3)	82 (98.8)	48 (100)	**0.013**
Non-binary	1 (0.7)	1 (1.2)	0	
Sexual Orientation				0.35
Homosexual	88 (67.2)	62 (74.7)	26 (54.2)	0.39
Bisexual	41 (31.3)	19 (22.9)	22 (45.9)	0.45
Pansexual	2 (1.5)	2 (2.4)	0	1.00
Sex Partner type in past 3 months (n, %)				
Men Only	107 (81.7)	70 (84.3)	37 (77.1)	0.35
Men & Women	24 (18.3)	13 (15.7)	11 (22.9)	
Number of Casual Sex Partners in the past 12 months (median, IQR)	4 (2-7)	4 (1-7)	4 (2.5-6.5)	0.39
Self-reported Knowledge of HIV status (n,%)	130 (99)	82 (98.8)	48 (100)	0.45
Correctly self-reported as HIV positive	27/32 (84.4)	18/21 (85.7)	9/11 (81.8)	1.00
Self-Reported Risk Factor In the past 3 months, (n,%)				
Sex under the influence of drugs	24 (18.4)	14 (16.9)	10 (20.9)	0.57
Sex at a sex-on-site premises	30 (22.9)	17 (20.5)	13 (27.8)	0.39
Sex with internet or app-sought partner	62 (47.4)	38 (45.8)	24 (50.0)	0.64
Accessed HIV PrEP	74 (56.5)	51 (61.4)	23 (47.9)	0.13
Condomless receptive anal sex with casual sex partner	72 (54.9)	61 (73.5)	11 (22.9)	**<0.001**
Insertive oro-anal sex (active rimming)	85 (64.9)	50 (60.3)	35 (72.9)	0.14
Receptive oro-anal sex (passive rimming)	72 (54.9)	53 (63.7)	19 (39.6)	**0.007**
Condomless receptive oro-penile sex (fellatio)	81 (61.9)	59 (71.8)	22 (45.9)	**0.004**
Sex with someone living in another SA province	33 (25.2)	20 (24.1)	13 (27.8)	0.70
Sex with someone living outside of the country	18 (13.8)	11 (13.3)	7 (14.6)	0.83
Self-reported STI in the past 6 months	29 (22.2)	19 (22.9)	10 (20.9)	0.79

Among participants presenting with male urethritis syndrome (MUS) at enrolment, an STI pathogen was detected in 87.5% (42/48) of urethral specimens (Table 2), with *N. gonorrhoeae* being the most common cause (32/42, 76.2%) followed by *C. trachomatis* (28.6%), and *M. genitalium* (26.2%). Urethral STIs were predominantly observed as mono-infections, with mixed infections (with two or three STIs) detected in 22.9% (11/48) of participants (Figure 1).

Table 2. Sexually transmitted pathogens detected in men who have sex with men (MSM) enroled in the 2023 surveillance study at the Engage Men's Health (EMH) Clinic in Melville, Johannesburg, South Africa.

	Patient without urethral discharge (N=83)		Patients with urethral discharge (N=48)		
Anatomical Site Sampled	**Pharynx**	**Rectum**	**Pharynx**	**Rectum**	**Urethra**
Total Number MSM with STI infections	2	34	1	16	42
Overall STI pathogen burden					
Neisseria gonorrhoeae (n/N,%)	1/83 (1.2)	18/79 (22.8)	1/48 (2.1)	13/46 (28.3)	32/48(66.7)
Chlamydia trachomatis (n/N,%)	1/83(1.2)	10/79 (12.7)	0	2/46 (4.3)	12/48 (25)
Trichomonas vaginalis (n/N,%)	0	0	0	0	0
Mycoplasma genitalium (n/N,%)	0	12/79 (15.2)	0	2/46 (4.3)	11/48 (22.9)

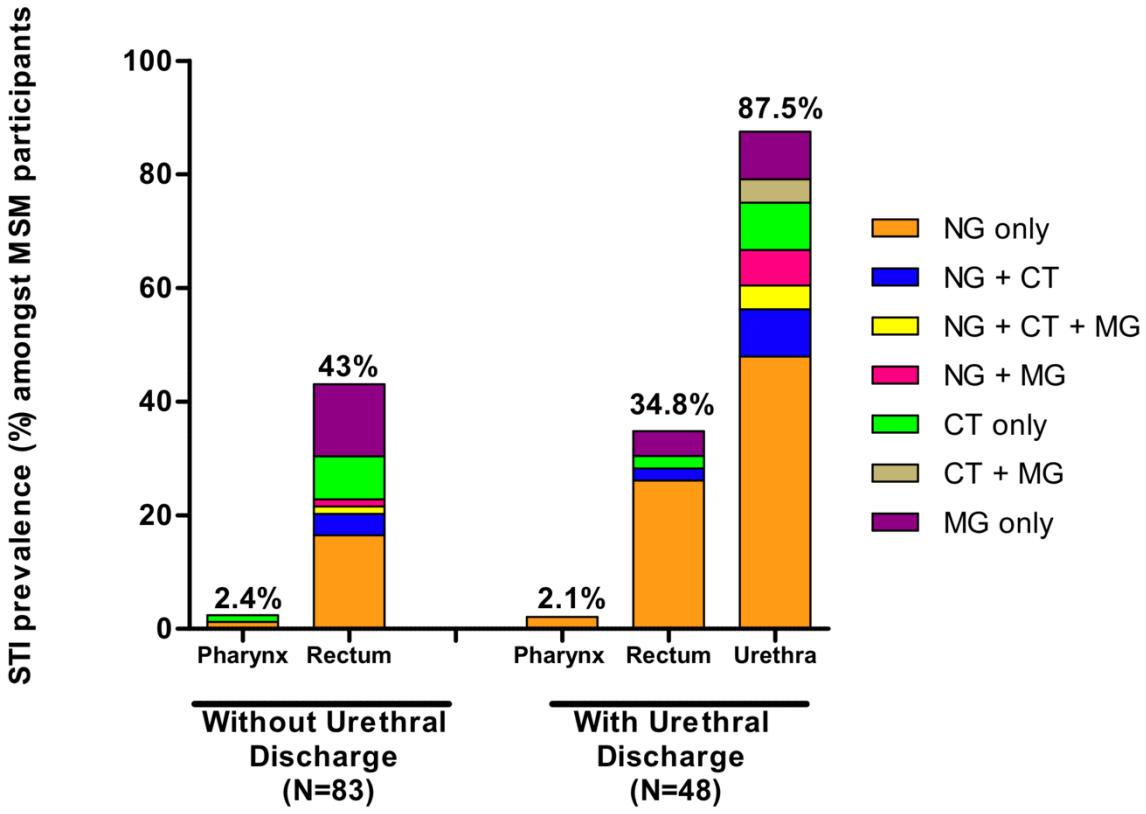

Figure 1. Prevalence of sexually transmitted infections (STIs) among men who have sex with men (MSM) by anatomical site of infection and urethral symptom status. The chart shows the overall proportion of MSM with a sexually transmitted infection (STI), as detected by molecular methods, as well as illustrates the aetiologies of mono- and mixed infections at sampled anatomical sites.

CT = *Chlamydia trachomatis*; MG = *Mycoplasma genitalium*; NG = *Neisseria gonorrhoeae*.

Neisseria gonorrhoeae culture isolation rates were low at extragenital sites, regardless of the presence of urethral symptoms, at 0% (0/2) and 19.4% (6/31) for pharyngeal and rectal *N.gonorrhoeae*, respectively. In contrast, the culture positivity from *N. gonorrhoeae* PCR-positive urethral specimens was 84.4 % (27/32). All gonococcal culture isolates, across both rectal and urethral anatomical sites, were sensitive to the third-generation cephalosphorins (ceftriaxone and cefixime). One urethral isolate had an azithromycin minimum inhibitory concentration (MIC) above the epidemiological cut-off of 1 mg/L (Table 3).

Table 3. *Neisseria gonorrhoeae* MICs to antimicrobial agents (N=33), Johannesburg, South Africa 2023.

	Patients without urethral discharge (N=5*)			Patients with urethral discharge (N=28^)		
Antimicrobial	**MIC_{50}**	**MIC_{90}**	**MIC range**	**MIC_{50}**	**MIC_{90}**	**MIC range**
Ceftriaxone (CRO)	0.003	0.004	<0.002-0.04	0.003	0.006	<0.002-0.016
Cefixime (CFM)	<0.016	<0.016	<0.016-0.016	<0.016	<0.016	<0.016-0.016
Azithromycin (AZM)	0.125	0.25	0.047-0.25	0.094	0.5	0.023-1.5

MIC, Minimum inhibitory concentration in mg/L
*All rectal *N.gonorrhoeae* isolates. ^ 1 rectal + 27 urethral *N.gonorrhoeae* isolates

Serological testing revealed that 24.4% (32/131) of participants had a reactive HIV antigen/antibody test, findings that did not differ by symptom status (22.9% vs 25.3% in MSM with and without urethral discharge, respectively). A high proportion of participants were reactive for specific treponemal antibodies (42.7%, 56/131), suggesting prior exposure to syphilis infection. RPR seropositivity amongst participants was 17.6%, representing MSM eligible for syphilis treatment. Classically, RPR titers ≤1:8 may be found in "serofast" individuals, that is, patients in whom RPR titres do not further decline despite successful treatment.[9] Amongst this study population, the overall proportion of MSM with RPR titres of >1:8 was 8.4% (11/131).

Discussion

The prevalence of extragenital STIs among MSM without urethral symptoms was high at 41% (34/83). These infections would go unidentified and untreated using the current syndromic management approach in this key population. The majority of extragenital infections were at the rectal site, and the most commonly detected rectal pathogen was *N. gonorrhoeae* in both subgroups. Rectal *M.genitalium* infection was observed in 15.2% (12/79) of MSM without urethral discharge; this is a significant increase from the 5.5% reported in our 2022 pilot study (p=0.03).[10] However, it must be emphasised that 12.7% (10/79) of these were mono-infections, with current guidelines advising against treatment for such asymptomatic infections due to rising antimicrobial resistance in this WHO-priority pathogen.[11] Despite the expected predominance of *N.gonorrhoeae* at the urethral site in symptomatic MSM, the overall prevalence of *M.genitalium* infections at this anatomical site (11/48) was significantly higher than that seen in the heterosexual male STI attendees recruited in Johannesburg in 2023 (22. 9% vs 2.7%, p<0.001).

All *N.gonorrhoeae* isolates in the 2023 survey were susceptible to the extended-spectrum cephalosporins, cefixime, and ceftriaxone, with a single urethral isolate displaying resistance to azithromycin. This suggests that the current first-line dual therapy regimen of ceftriaxone (250mg)-azithromycin (1g) is still adequate.[4] Ceftriaxone-resistant (FC428 clone) as well as extensively drug-resistant (resistance to both ceftriaxone and azithromycin) *N. gonorrhoeae* strains are circulating globally and have been linked to travel and sexual networks in Southeast Asia and Europe.[12] Locally, reports of azithromycin resistance in South African *N. gonorrhoae* isolates are emerging.[13] This links with participation in international sexual networks as self-reported by 13.8% of participants, and thus the potential for importation of resistant strains highlights the importance of continued and expanded STI surveillance in this key population.

HIV antigen/antibody test reactivity was detected in approximately a quarter of participants. Although this is high in comparison to the 11.5% HIV seropositivity reported among adult men (≥15 years) in the general population[14], it is within the ranges (13.6%-49.5%) reported in MSM across the country.[15] Importantly, 84.4% of these participants correctly self-disclosed as HIV positive, a finding that largely mirrors knowledge of HIV status among men in the general population (85.1%), although linkage to care was higher in the MSM cohort (100% vs 90.1%)[12]. Strategies are needed to increase the uptake of HIV testing services among MSM.

RPR seropositivity among those tested was 17.6%. These at-risk men would require treatment, especially if they have no prior history of treatment for syphilis. Due to global supply shortages of benzathine benzylpenicillin (benzathine penicillin G, BPG), non-pregnant adults with syphilis are treated with doxycycline. However, the extended oral doxycycline regimen (100mg 12-hourly orally for 14-30 days) required to treat the *Treponema pallidum* infection is often associated with gastrointestinal adverse effects and may result in suboptimal adherence.[7]

The study has numerous limitations. Importantly, recruitment from a single clinic limits generalisability to MSM across South Africa. Furthermore, as much of our demographic and behavioural data were self-reported, these outcomes are subject to recall and social desirability bias. In our questionnaire, we did not include variables relating to sexual position (top, bottom, versatile) preference with the most recent sexual partner, which may provide insights into the lower rates of rectal STIs in MSM with urethritis. As our serological screening methods are used for surveillance purposes only, HIV reactivity is not confirmed using additional testing procedures, and thus

care has been taken to not report these as "HIV positive." HIV viral load testing is not performed as part of routine STI surveillance, and hence data on the third 95-95-95 target, namely viral suppression as defined as HIV RNA <1000 copies/ml, is lacking.

Conclusion

This study was the first to investigate STI aetiologies as well as *N.gonorrhoeae* AMR amongst MSM with and without urethral discharge as part of the NICD's routine STI surveillance program. The burden of extragenital STIs and active syphilis in MSM is high, particularly in MSM without urethral symptoms. Our data reaffirms that the syndromic approach is inadequate for STI identification and treatment in this key population, highlighting the need for routine aetiological and syphilis serological screening. This study further revealed that STI aetiologies amongst MSM with urethritis differ from those detected amongst symptomatic heterosexual men, with *M.genitalium* implicated as an important pathogen. These findings underscore the importance of including different population groups in surveillance programs.

Recommendations

- Aetiological STI screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in all MSM at the rectal anatomical site should be provided as a routine service to this key population, at least annually.
- Syphilis serological testing should be offered to all MSM at least annually. The provision of dual HIV-syphilis rapid diagnostic tests (RDTs) for use in this key population will allow this testing to be integrated into existing HIV services.
- After pregnant women and their children, MSM should be prioritised for receipt of benzathine penicillin G to curb the high rates of active syphilis in his key population.
- A single STI surveillance sentinel site for MSM is inadequate; expansion of this programme to at least another clinical site in the country is needed.
- Other key populations at high risk of acquiring and transmitting STIs, such as female and male sex workers, should be included in STI surveillance expansion efforts.

Further improvements and future research

- Improvements in *Neisseria gonorrhoeae* culture isolation rates from extragenital sites are required
- Whole genome sequencing of cultured isolates for genomic surveillance and epidemiology studies to better describe local strains, understand transmission networks, as well as identify and characterise AMR determinants in *N.gonorrhoeae*
- Molecular characterisation and investigation of AMR-associated mutations in *M.genitalium* strains identified in this key population

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Ethical considerations

Ethical approval for this study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), clearance number: M210642.

Conflicts of interest

The authors declare no competing interests.

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