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MAJOR ARTICLE

Incidence and Risk Factors for Early Syphilis Among Men Who Have Sex With Men in Australia, 2013–2019: A Retrospective Cohort Study

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Background. We aimed to examine the incidence of syphilis in men who have sex with men (MSM) and identify subgroups of MSM at a higher risk of syphilis infection.

Methods. We conducted a retrospective cohort study of MSM attending a sexual health clinic in Australia, during 2013–2019, who had at least 2 syphilis serological tests during the study period. The incidence of syphilis was expressed as per 100 person-years. A cox regression analysis was conducted to identify risk factors for syphilis.

Results. A total of 24 391 individual MSM (75 086 consultations) were included. A total of 1404 new syphilis cases were diagnosed with an incidence of 3.7/100 person-years (95% confidence interval, 3.5–3.9). Syphilis incidence was higher in MSM with human immunodeficiency virus ([HIV] 9.3/100 person-years) than in MSM taking HIV pre-exposure prophylaxis (PrEP) (6.9/100 person-years) or HIV-negative MSM not taking PrEP (2.2/100 person-years). Risk factors associated with high incidence of syphilis included the following: MSM with HIV (adjusted hazard ratio [aHR] 2.7), MSM taking HIV PrEP (aHR 2.1), past history of syphilis infection (aHR 2.4), injecting drug use (aHR 2.7), condomless anal sex (aHR 1.7), >4 sexual partners in the last 12 months (aHR 1.2), and concurrent sexually transmitted infection (chlamydia and gonorrhoea) (aHR 1.6).

Conclusions. The incidence of syphilis remains high among MSM, particularly in subgroups with associated risk factors for syphilis infections. These data highlight the need for biomedical and behavioral interventions to be targeted to subgroups of MSM at the highest risk of syphilis infection.

Keywords. men who have sex with men; risk factors; sexually transmitted infections; syphilis; incidence.

Syphilis is a sexually transmitted infection (STI) caused by the spirochaete *Treponema pallidum* and remains a global public health problem [1]. Untreated syphilis can lead to serious complications, such as neurosyphilis, ocular syphilis, and congenital syphilis. Early diagnosis and treatment are keys to reducing morbidity and transmission. In Australia, syphilis disproportionately affects men who have sex with men (MSM) [2, 3]. The current Australian STI screening guidelines recommend regular 3-monthly STI screening, including syphilis serology, among MSM [4], which is one key strategy to control syphilis [5].

However, there is still an ongoing epidemic of syphilis despite an increase in screening among MSM [2, 6, 7]. A previous Australian study has shown that 64% (n = 3081) of the notified syphilis cases in Victoria were in MSM, highlighting a burden of infection in this key population [3]. The STI prevention strategies such as condom use, behavior counseling, and regular screening have limited success in the prevention of syphilis, and other novel interventions may be needed to effectively control the syphilis epidemic [8].

Biomedical interventions using doxycycline either as pre-exposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for STI have been studied in recent years, especially for high-risk individuals [9, 10]. These studies have demonstrated significant effectiveness and tolerability against common STIs, including syphilis [9, 10]. However, doxycycline prophylaxis has been a topic of debate among researchers and healthcare providers due to concerns over antimicrobial resistance. Understanding the characteristics and subgroups of MSM who are at high risk of syphilis infection could help identify men who will most likely benefit from the doxycycline prophylaxis.

Studies examining the risk of syphilis infection in MSM often focused on men with human immunodeficiency virus (HIV) or men taking HIV PrEP because they are considered populations at a higher risk of syphilis infection [11–20]. Because these studies specifically focused on specific groups, the findings might not apply to other MSM without the characteristics

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examined in these studies. Moreover, some studies were conducted before HIV PrEP became widely available, and, therefore, it is important to provide an update on the changes in the epidemiology of syphilis and associated risk factors in the HIV PrEP era [11, 12]. In Australia, public sexual health clinics are ideal settings for studying risk factors of syphilis in both the general and high-risk MSM populations, due to the easy accessibility by MSM, routine collection of sexual risk data, and repeated STI testing, including syphilis as a routine practice.

We aimed to examine (1) the overall incidence rate of MSM attending a sexual health clinic from 2013 to 2019, (2) the incidence rates stratified by risk factors, and (3) the risk factors for syphilis infection.

METHODS

Study Population and Setting

This was a retrospective cohort study at the Melbourne Sexual Health Centre (MSHC) between January 2013 and December 2019. The MSHC is a public sexual health and HIV clinic in the state of Victoria, Australia and provides approximately 50 000 consultations per year. The clinic has an electronic medical record system that stores demographic and epidemiological data. New clients and returning clients who have not been seen for more than 3 months are routinely asked to complete a questionnaire using computer-assisted self-interview (CASI) upon arrival at the clinic. We included MSM (defined as men who had sex with men in the last 12 months) aged 16 years or older, who visited the clinic 2 or more times and had at least 2 syphilis serological tests within the study duration. Transgender individuals were excluded because their gender and sexual practice could not be clarified by CASI. We excluded first-time single visits without previous syphilis serology at MSHC. We excluded duplicate diagnoses that were created when some clients returned for syphilis treatment.

Data Collection

We extracted data on clients' demographic characteristics (eg, age, country of birth), sexual practices (eg, number of sexual partners and condom use), HIV status, use of HIV PrEP, self-reported past history of syphilis infection, and concurrent diagnosis of HIV and bacterial STIs (gonorrhoea and chlamydia) from routinely collected health data.

Human Immunodeficiency Virus and Sexually Transmitted Infection Diagnoses

Early syphilis included primary, secondary, or early latent syphilis (<2 years) as per the definition by the Australian Department of Health [21]. All syphilis cases were diagnosed using *Treponema*-specific tests (*T pallidum* enzyme immunoassay [EIA] or chemiluminescence immunoassay [CLIA] and *T pallidum* particle agglutination assay [TPPA]) and non-*Treponema*-specific test (the rapid plasma reagin [RPR] test). A new early infectious syphilis was defined as (1) any positive *Treponema*-specific test (CLIA or EIA and TPPA) and a positive RPR compared with a previous negative result within the last 2 years, or (2) positive *T pallidum* polymerase chain reaction (PCR) from any suspected syphilis lesion independent of the syphilis serology result, or (3) a 4-fold rise in RPR titer from a previous serology after successful treatment of syphilis infection [21] (Figure 1). The subsequent syphilis infections after a first syphilis infection diagnosed during the study period are called repeated infections, and this could occur multiple times. All syphilis cases were reviewed by 2 sexual health clinicians independently, and any discrepancies were resolved by consensus.

Chlamydia diagnoses included infections at any anatomical sites (ie, oropharynx, urethra and/or anorectum) detected by nucleic acid amplification test using Aptima Combo 2 (AC2) assay (Hologic Panther System; Hologic, San Diego, CA, USA). Gonorrhoea infections at any anatomical sites (ie, oropharynx, urethra and/or anorectum) were diagnosed using the same method as chlamydia infection (AC2 assay) from March 2015, whereas modified Thayer Martin medium for gonorrhoea culture was used to diagnosed gonorrhoea before March 2015 [22]. Individuals who were diagnosed with concurrent gonorrhoea or chlamydia at multiple anatomical sites on the same day were considered a single infection in this analysis. The HIV infections were diagnosed using DiaSorin Liaison XL Murex HIV Ab/Ag CLIA (fourth generation) assay from April 2014 and Abbott Murex HIV-1 2.0 EIA (third generation) before April 2014 and confirmed by the Western blot assay.

Statistical Analysis

The primary outcome was the incidence of early syphilis infection during the observation period. We calculated the incidence of early syphilis by dividing the number of new cases by the number of person-years-at-risk and expressed as per 100 person-years. We defined person-years-at-risk as the time between 2 syphilis tests. Individuals were censored if they were diagnosed with early syphilis; however, they became at risk again after treatment. Individuals were censored at the date of their last syphilis test if they had never been diagnosed with early syphilis during the observation period. For individuals who had multiple syphilis diagnoses within 30 days, only the first diagnosis was included and the subsequent syphilis diagnoses within 30 days were excluded. The 95% confidence intervals (CIs) of incidence were calculated from a Poisson distribution.

Univariable and multivariable Cox regression analyses were performed to identify the risk factors associated with incident early syphilis infection. We included factors based on existing literature [11–17] or if its incidence rate was higher than the overall incidence in the current study. Factors with $P < .20$ in the univariable analysis were considered confounding factors and were included in the multivariable analysis [23]. Crude

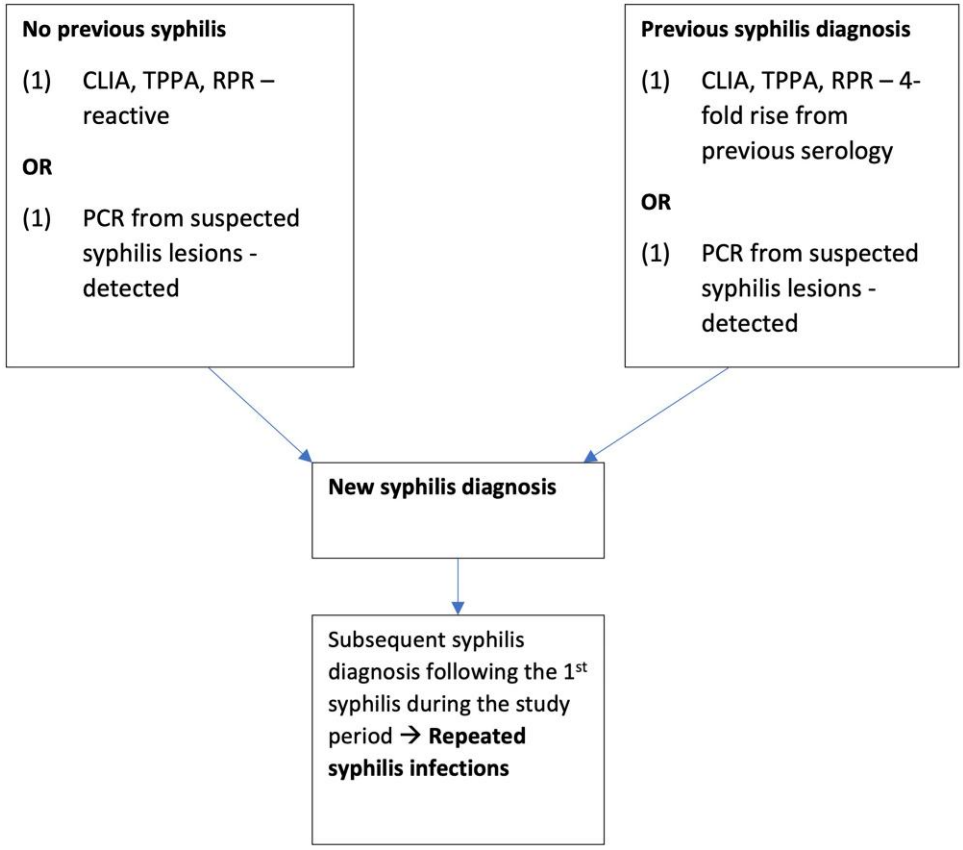

Figure 1. Algorithm for syphilis case definition. CLIA, chemiluminescence immunoassay; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TPPA, *Treponema pallidum* particle agglutination assay.

and adjusted hazard ratios (aHRs) and their corresponding 95% confidence intervals (CIs) were calculated [24].

Descriptive data were presented in percentage and median with interquartile range (IQR) as appropriate. All statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX, USA).

Ethics Approval

Ethical approval was obtained from the Alfred Hospital Ethics committee, Melbourne, Australia (Project 449/18).

RESULTS

Between January 2013 and December 2019, there were 162 781 consultations for MSM, and 106 141 (65%) consultations were from individuals who had syphilis serology at these consultations. Among these 106 141 consultations, there were 1982 syphilis diagnoses. We excluded 31 055 consultations, including 23 410 consultations with no previous syphilis test results, and 7645 duplicate consultations from the same individual on the same day (ie, different clinicians saw the same individual). Among these 23 410 consultations, 578 syphilis cases were diagnosed at their first-time single visit with no preceding serology.

The final analysis included 24 391 individual MSM with a total of 75 086 consultations, which had 2 or more syphilis serology during the study period. A total of 38 396 person-years of follow-up and 1404 early syphilis cases were included in the study (Figure 2).

Of the 24 391 MSM, the median age at baseline was 31 (IQR, 16–89) years (Table 1). Among these MSM, 1623 (7%) were men with HIV, 873 (4%) were men taking HIV PrEP, and 21 895 (89%) were men not taking HIV PrEP or without HIV. Only 1467 (6%) had a past history of syphilis infection (Table 1).

A total of 400 men were diagnosed with 1404 early syphilis cases, which included 400 (28%) primary syphilis, 295 (21%) secondary syphilis, and 705 (51%) early latent syphilis.

The overall incidence of syphilis was 3.7 per 100 person-years (95% CI, 3.5–3.9) (Table 2). Men with HIV had the highest incidence of syphilis (9.3 per 100 person-years), followed by men taking HIV PrEP (6.9 per 100 person-years), and men who did not have HIV and were not taking HIV PrEP (2.2 per 100 person-years).

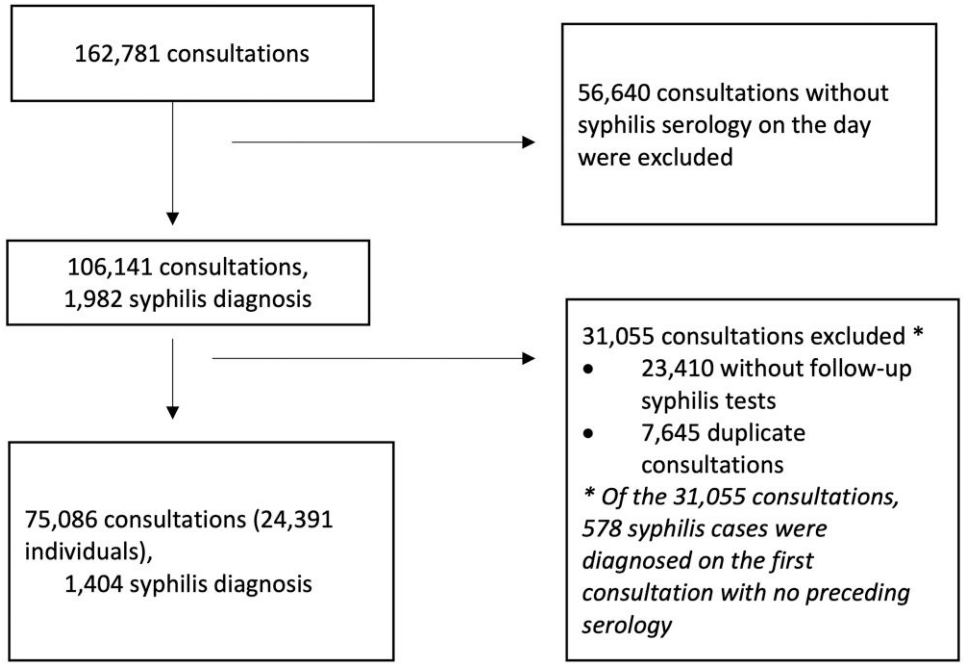

Figure 2. Flowchart of study recruitment.

In the multivariable Cox regression analysis, the following factors were independently associated with incident early syphilis infection: men with HIV (aHR = 2.7; 95% CI, 2.3–3.1); men taking HIV PrEP (aHR = 2.1; 95% CI, 1.8–2.5); men with a history of syphilis infection (aHR = 2.4; 95% CI, 2.0–2.9); men who had injected drug in the last 12 months (aHR = 2.7; 95% CI, 2.1–3.4); men who had injected drugs more than 12 months ago (aHR = 1.9; 95% CI, 1.2–3.0); condomless anal sex with male partners in the last 12 months (aHR = 1.7; 95% CI, 1.4–2.1); having 4 or more sexual partners in the last 12 months (aHR = 1.2; 95% CI, 1.0–1.4); and concurrent chlamydia (aHR = 1.6; 95% CI, 1.4–1.8) or gonorrhoea (aHR = 1.6; 95% CI, 1.3–1.8) infection (Table 3). The association between age and incident syphilis infections became nonsignificant after controlling for other confounding factors.

Concurrent HIV infection was a risk factor for syphilis infection on univariable analysis (HR 2.9; 95% CI, 2.1–4.0; $P < .001$) compared to those without HIV infection. It was not included in the multivariable Cox regression analysis because the analysis already included men with HIV infection.

We performed another Cox regression analysis of risk factors without men with HIV infection due to large missing data on behavioral and sexual risks in this group. The analysis identified the same risk factors as Table 3 for syphilis infection (men taking HIV PrEP, men with a history of syphilis infection, men who had injected drug in the last 12 months, men who had injected drugs more than 12 months ago, condomless anal sex with male partners in the last 12 months, having 4 or more sexual partners in the last 12 months, and concurrent chlamydia or gonorrhoea infection). Concurrent HIV infection was not a risk factor for syphilis infection in this multivariate analysis.

Table 4 shows the risk factors for repeated and first syphilis infection during the study period. Of the 1404 syphilis cases, 511 (36%) cases were repeated infections with an incidence of 1.3 (95% CI, 1.2–1.5) per 100 person-years, whereas 893 (64%) cases were syphilis cases diagnosed for the first time during the study period. Among the repeated infections, 300 cases (59%) had an infection twice, 162 cases (32%) had it 3 times, and 40 cases (8%) had it 4 times. The median time between each infection was 1.2 years (IQR, 0.7–2.1 years). Repeated infections were more common in men with HIV ($P = .001$).

DISCUSSION

Our study showed a high incidence of syphilis among MSM and identified several risk factors associated with a higher incidence of syphilis. We found that the risk of syphilis infection was the highest in men with HIV and men who were injecting drugs, followed by men taking HIV PrEP, men with a past history of syphilis, with concurrent gonorrhoea or chlamydia infections, practicing condomless anal sex, and with more than 4 sexual partners in the last 12 months. Men with HIV had the highest syphilis incidence rate in addition to having the highest risk of syphilis infection compared with men taking HIV PrEP and men not taking HIV PrEP. Identifying men with risk factors for syphilis infection is an important step in

Table 1. Baseline Characteristics of 24 391 Men Who Have Sex With Men Attending the Melbourne Sexual Health Centre, 2013–2019

	Number (N = 24 391)	Percentage (%)
Age, median (interquartile range) (years)	31 (16–89)	
Sexual Practices in the Last 12 Months		
Had sex with men only	21 167	86%
Had sex with both men and women	3224	14%
Use of Injecting Drugs		
Never	19 999	82%
Yes, in the last 12 months	411	2%
Yes, more than 12 months ago	264	1%
Missing[a]	3717	15%
HIV and PrEP Status		
HIV positive (men with HIV)	1623	7%
HIV negative, not taking HIV PrEP	21 895	89%
HIV negative, taking HIV PrEP	873	4%
Past History of Syphilis Infection		
Yes	1467	6%
No	9358	38%
Missing[a]	13 566	56%
Number of Sexual Partners in the Last 12 Months		
≤4	10 850	44%
>4	11 748	48%
Missing[a]	1793	8%
Condom Use in the Last 12 Months		
Always use condoms	7389	30%
Condomless anal sex	12 542	51%
No penetrative sex	1179	5%
Missing[a]	3281	14%

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis.

[a]Missing data due to clients declined to disclose, chose not to complete the computer-assisted self-interview, or they did not know the answer.

delivering focused interventions to reduce future infections. Specifically, the incidence within higher risk groups will assist with the relative benefit or harm associated with doxycycline prophylaxis, which remains controversial [25].

Our study showed a higher risk of acquiring early syphilis among men with HIV compared with those who did not have with HIV, and this finding was consistent with previous studies reporting a high incidence of syphilis among men with HIV [11, 14, 26]. Furthermore, we observed that repeated syphilis infections were more common among men with HIV than men who did not have HIV. The reasons for high incidence of syphilis in men with HIV could be multifactorial. A Swiss HIV Cohort Study reported that past history of syphilis, condomless anal sex, and being currently on antiretroviral therapy (ART) were associated with syphilis infection among men with HIV [14]. There is likely serosorting among MSM with HIV and taking ART, together with other sexual risk behaviors, such as condomless anal sex, that are likely to increase risk for syphilis infection in this subgroup of MSM [27]. Studies in Australia have reported an increase in sexual mixing between HIV serodiscordant MSM couples (from 0% to 12.5% between 2011 and 2018), condomless anal sex, and casual sexual partners [27, 28]. Moreover, increased syphilis testing in men with HIV by adding syphilis testing to routine monitoring of HIV treatment blood tests have shown to increase the detection of syphilis infection [6, 7].

We reported a high incidence of syphilis among men taking HIV PrEP, a consistent finding with other studies among PrEP users [29, 30]. The PrEPX study in Victoria, Australia reported that the syphilis incidence in MSM taking HIV PrEP between 2016 and 2018 was 8 per 100 person-years, which was similar to our study [29]. Significant changes in the pattern of sexual mixing by HIV status and HIV PrEP use among MSM partnerships over time have been observed, and these may have increased the likelihood of acquiring STIs including syphilis. Genomic studies of *T pallidum* in Australia showed that transmission occurred across different sexual networks among MSM, indicating high interconnectivity among their sexual networks [31].

In addition to standard public health measures for syphilis control, there should be a focus on novel interventions to target subgroups of MSM with risk factors. The findings from our study can provide clinical guidance around identifying people who are at higher risk of syphilis so that targeted interventions can be used. Condom use is one of the effective interventions to prevent syphilis; however, behavioral surveillance has reported that there has been an increase in condomless anal sex in MSM (ie, from 37% in 2014% to 62% in 2019) [28]. Therefore, promoting condom use in MSM might not be effective for syphilis control [32, 33].

Early detection of syphilis by regular STI screening, and timely treatment, remain the principal syphilis control approaches [6, 34], although screening alone might not be sufficient to detect incident syphilis diagnosed between the regular screening [30]. Studies examining doxycycline prophylaxis for syphilis prevention have reported promising results on efficacy [9, 10]. A recent US trial has shown that the use of doxycycline prophylaxis can reduce the risk of syphilis by 70% [9]. Although the use of doxycycline prophylaxis has not been recommended in most guidelines, past studies have shown that approximately 10% of MSM taking HIV PrEP reported using antibiotic prophylaxis for STIs [35, 36]. The effect on the gut microbiome and the potential rise of antimicrobial resistance should also be considered when prescribing doxycycline prophylaxis. It is important for healthcare providers to provide appropriate guidance on the use of antibiotic prophylaxis by identifying risk factors for syphilis and selecting those who will benefit most.

The greatest strength of our study was that this was a cohort study with a large sample size. However, there were several limitations in the study. First, there was a large amount missing data on behavioral and sexual risks, especially in men with HIV, which could bias the outcomes. This was mainly due to

Table 2. The Incidence Rate of Syphilis Infection Among Men Who Have Sex With Men Attending the Melbourne Sexual Health Centre Between 2013 and 2019

	No. of Syphilis Cases	Person-Years	Incidence Rate (100 Person-Years) [95% CI]
Total	1404	38 396	3.7 [3.5–3.9]
Sexual Practices in the Last 12 Months			
Having sex with men only	1360	34 804	4.5 [3.7–4.1]
Having sex with both men and women	44	3592	1.5 [1.2–1.6]
Age at Consultation, Years			
16–24	136	5169	2.6 [2.2–3.1]
25–29	285	9204	3.1 [2.8–3.5]
30–35	372	9411	4.0 [3.6–4.4]
>35	611	14 612	4.2 [3.9–4.5]
HIV and PrEP Status			
HIV positive (men with HIV)	513	5523	9.3 [8.5–10.1]
HIV negative, not taking HIV PrEP	635	29 152	2.2 [2.0–2.4]
HIV negative, taking HIV PrEP	256	3720	6.9 [6.1–7.8]
Past History of Syphilis Infection			
No	954	22 865	4.2 [3.9–4.4]
Yes	252	3434	7.3 [6.5–8.3]
Missing[a]	198	12 097	1.6 [1.4–1.9]
Injecting Drugs Use			
Never	525	25 769	2.0 [1.9–2.2]
Yes, in the last 12 months	94	657	14.3 [11.7–17.5]
Yes, more than 12 months ago	19	335	5.7 [3.6–8.9]
Missing[a]	766	11 634	6.6 [6.1–7.1]
Condomless Anal Sex With Men in the Last 12 Months for Anal Sex With Men			
No	106	8342	1.3 [1.1–1.5]
Yes	595	17 478	3.4 [3.1–3.7]
No penetrative sex	4	900	0.4 [0.2–1.2]
Missing[a]	699	11 676	6.0 [5.6–6.4]
Number of Male Partners in the Last 12 Months			
4	260	13 018	2.0 [1.8–2.3]
>4	513	16 378	3.1 [2.9–3.4]
Missing[a]	631	8999	7.0 [6.5–7.6]
Concurrent Chlamydia Infection			
Negative	1061	32 838	3.2 [3.0–3.4]
Positive	266	3506	7.6 [6.7–8.6]
Not tested	77	2052	3.8 [3.0–4.7]
Concurrent Gonorrhoea Infection			
Negative	1052	32 330	3.3 [3.1–3.5]
Positive	269	3754	7.2 [6.4–8.1]
Not tested	83	2312	3.6 [2.9–4.5]
Concurrent HIV Diagnosis			
Negative	1050	33 251	3.2 [3.0–3.4]
Positive	39	437	8.9 [6.5–12.2]
Not tested	315	4708	6.7 [6.0–7.5]

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis.

[a]Missing data due to clients declined to disclose, chose not to complete the computer-assisted self-interview, or they did not know the answer.

incomplete routinely collected health data. People with HIV and attending our clinic for HIV care are not usually required to complete the routine questionnaires using CASI. People with HIV might have been concerned about being judged by clinicians if they reported a high number of partners or condomless sex, which might be a factor in missing data. We considered all missing data in our analyses to minimize the selection or reporting bias (by creating a variable). Second, sexual health clinic attendees are more likely to be sexually active and, therefore, at higher risk of STIs, compared with the general population of MSM. Using data from a sexual health clinic might introduce bias into the epidemiological data, and the findings might not represent all MSM living in Victoria, Australia or other settings.

Table 3. Univariable and Multivariable Hazard Ratio of Syphilis Incidence by Risk Factors for Syphilis Infection

Risk Factors	Hazard ratio [95% CI]	*P* Value	Adjusted HR [95% CI]	*P* Value
Age at Consultation, Years				
16–24	1 (ref)		1 (ref)	
25–29	1.2 [0.9–1.5]	.090	1.0 [0.8–1.2]	.990
30–35	1.5 [1.3–1.9]	<.001	1.1 [0.9–1.3]	.533
>35	1.6 [1.3–1.9]	<.001	1.0 [0.8–1.2]	.738
HIV and PrEP Status				
HIV negative, not taking HIV PrEP	1 (ref)		1 (ref)	
HIV negative, taking HIV PrEP	3.5 [3.0–4.0]	<.001	2.1 [1.8–2.5]	<.001
HIV positive (men with HIV)	4.5 [4.0–5.0]	<.001	2.7 [2.3–3.1]	<.001
Past History of Syphilis Infection				
No	1 (ref)		1 (ref)	
Yes	1.7 [1.5–2.0]	<.001	2.4 [2.0–2.9]	<.001
Missing[a]	0.4 [0.3–0.4]	<.001	0.9 [0.7–1.0]	.099
Injecting Drug Use				
No	1 (ref)		1 (ref)	
Yes, in the last 12 months	7.1 [5.7–8.8]	<.001	2.7 [2.1–3.4]	<.001
Yes, more than 12 months ago	2.8 [1.8–4.4]	<.001	1.9 [1.2–3.0]	.007
Missing[a]	3.5 [3.2–4.0]	<.001	2.4 [2.0–3.0]	<.001
Condomless Anal Sex With Men in the last 12 Months for Anal Sex With Men				
No	1 (ref)		1 (ref)	
Yes	2.7 [2.2–3.3]	<.001	1.7 [1.4–2.1]	<.001
No penetrative sex	0.4 [0.1–1.0]	.041	0.4 [0.1–1.0]	.055
Missing[n]	5.0 [4.1–6.2]	<.001	1.6 [1.1–2.1]	.006
Number of Male Partners in the Last 12 Months				
4	1 (ref)		1 (ref)	
>4	1.6 [1.4–1.8]	<.001	1.2 [1.0–1.4]	.036
Missing[a]	4.0 [3.4–4.6]	<.001	1.4 [1.1–1.9]	.009
Concurrent Chlamydia Infection				
Negative	1 (ref)		1 (ref)	
Positive	2.3 [2.0–2.7]	<.001	1.6 [1.4–1.8]	<.001
Not tested	1.1 [0.8–1.4]	.559	0.5 [0.2–1.0]	.044
Concurrent Gonorrhoea Infection				
Negative	1 (ref)		1 (ref)	
Positive	2.2 [1.9–2.6]	<.001	1.6 [1.4–1.8]	<.001
Not tested	1.0 [0.8–1.3]	.788	0.7 [0.4–1.5]	.394

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; PrEP, pre-exposure prophylaxis.

[a]Missing data due to clients declined to disclose, chose not to complete the computer-assisted self-interview, or they did not know the answer.

Third, the calculation of syphilis incidence in our study relied heavily on repeat syphilis testing among individuals. Biases could have occurred by excluding single visits during the observation period and those who were diagnosed with syphilis during their very first visit. Moreover, this could also lead to overrepresenting men who were at risk. Fourth, the proportion of men taking HIV PrEP was small in our study sample, which might have affected the outcomes. The small number could be due to HIV PrEP only becoming available on the Australian Pharmaceutical Benefits Scheme (PBS) in April 2018, and there were only 20 months in our study since PrEP had been widely implemented. This short period may not be able to capture the incidence. Moreover, the clinic has limited capacity for routine PrEP appointments, which might have contributed to a small percentage of men taking HIV PrEP in our study. Fifth, repeated syphilis infection is defined as a 4-fold increase in RPR titer after an appropriate 4-fold reduction after treatment. However, we might have underestimated the frequency of repeated infections if someone is re-exposed after successful treatment before the RPR titers have resolved appropriately. Finally, we could have underestimated the incidence because we only included data from our clinic. Some individuals might have been tested for or diagnosed with syphilis in other settings, such as general practices, during the observation period.

Our study has demonstrated that syphilis cases continue to increase in MSM, and more so in those with risk factors for syphilis infections. A reduction of syphilis incidence will require interventions that effectively address these risk factors. Accessible healthcare, including STI screening and treatment for high-risk populations, is an important public health strategy in syphilis control. Health promotion among the high-risk populations and education of clinicians to promote regular STI

Table 4. Comparison of Risk Factors Between First Syphilis Infection in the Study Period and Repeated Infections Among MSM—2013 and 2019

	Repeated Syphilis Infection		First Syphilis Infection	
	Numbers of Cases (N = 511)	Percentage (%)	Number of Cases (N = 893)	Percentage (%)
Men who have sex only with men	506	99	854	96
Men who have sex with men and women	5	1	39	4
Age at Consultation, Years				
16–24	25	5	111	12
25–29	86	17	199	22
30–35	145	28	227	25
>35	255	50	356	41
HIV and PrEP Status				
HIV positive (men with HIV)	274	53	239	27
HIV negative, not taking HIV PrEP	152	30	483	54
HIV negative, taking HIV PrEP	85	17	171	19
Past History of Syphilis Infection[a]				
No	326	64	628	71
Yes	125	24	127	14
Missing[b]	60	12	138	15
Injecting Drug Use				
No	138	27	387	43
Yes, in the last 12 months	53	10	41	5
Yes, more than 12 months ago	6	1	13	1
Missing[b]	314	62	452	51
Condomless Anal Sex With Men in the Last 12 Months for Anal Sex With Men				
No	31	6	75	8
Yes	191	37	404	45
No penetrative sex	1	0.2	3	0.3
Missing[b]	288	57	411	46
Number of Male Partners in the Last 12 Months				
4	82	16	178	20
>4	169	33	344	39
Missing[b]	260	51	371	43
Concurrent Chlamydia Infection				
Negative	355	70	706	79
Positive	118	23	148	17
Not tested	38	7	39	4
Concurrent Gonorrhoea Infection				
Negative	343	67	709	79
Positive	126	25	143	16
Not tested	42	8	41	5
Concurrent HIV Diagnosis				
Negative	320	63	730	82
Positive	12	2	27	3
Not tested	179	35	136	15

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis;

[a]Self-reported history of syphilis infection.

[b]Missing data due to clients declined to disclose, chose not to complete the computer-assisted self-interview, or they did not know the answer.

screening in line with current STI guidelines might improve testing rates. Although regular STI screening (ie, 3-monthly) has been the main approach for syphilis control, the ongoing rise in syphilis cases and diagnosis of syphilis in the interval periods between screenings have prompt calls for interventions that not do not rely on condom use [29, 30]. These interventions include the use of PCR on samples from the oral cavity and anus in asymptomatic people and anal self-examination in MSM who practice receptive anal sex for early detection of syphilis [37–41].

CONCLUSIONS

In summary, our study has identified several key risk factors for syphilis infection, which can guide syphilis control at both the

individual and population levels. Understanding risk factors for the high incidence of syphilis among subgroups of MSM will enable us to tailor interventions to improve syphilis control among these subgroups. These risk factors can be integrated into artificial intelligence modeling to predict the risk of syphilis infection for individuals and, perhaps, develop risk-scoring tools to guide intervention models appropriate for syphilis control.

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