Clinical Infectious Diseases

MAJOR ARTICLE

Increased Syphilis Testing of Men Who Have Sex With Men: Greater Detection of Asymptomatic Early Syphilis and Relative Reduction in Secondary Syphilis

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(See the Editorial Commentary by Klausner on pages 396–7.)

Background. Syphilis rates have increased markedly among men who have sex with men (MSM) internationally. We examined trends in syphilis testing and detection of early syphilis among MSM in Australia.

Methods. Serial cross-sectional analyses on syphilis testing and diagnoses among MSM attending a national sentinel network of 46 clinics in Australia between 2007 and 2014.

Results. 359 313 clinic visits were included. The proportion of MSM serologically tested for syphilis annually increased in HIV-negative (48% to 91%; $P_{trend} < .0001$) and HIV-positive MSM (42% to 77%; $P_{trend} < .0001$). The mean number of tests per man per year increased from 1.3 to 1.6 in HIV-negative MSM ($P_{trend} < .0001$) and from 1.6 to 2.3 in HIV-positive MSM ($P_{trend} < .0001$). 2799 and 1032 syphilis cases were detected in HIV-negative and HIV-positive MSM, respectively. Among HIV-negative MSM, the proportion of infections that were early latent increased from 27% to 44% ($P_{trend} < .0001$), while the proportion that were secondary decreased from 24% to 19% ($P_{trend} = .030$). Among HIV-positive MSM, early latent infections increased from 23% to 45% ($P_{trend} < .0001$), while secondary infections decreased from 45% to 26% ($P_{trend} = .0003$). Among HIV-positive MSM, decreasing secondary syphilis correlated with increasing testing coverage ($r = -0.87$; $P = .005$) or frequency ($r = -0.93$; $P = .001$).

Conclusions. Increases in syphilis screening were associated with increased detection of asymptomatic infectious syphilis and relative falls in secondary syphilis for both HIV-positive and HIV-negative MSM nationally, suggesting interruption of syphilis progression.

Keywords. syphilis; screening; men who have sex with men.

In many countries, rates of syphilis among men who have sex with men (MSM) have been rising since the beginning of the 21st century and are now at the highest levels in decades in several regions [1]. In many countries, syphilis infections are overrepresented among human immunodeficiency virus (HIV)–positive MSM. Factors that have been proposed for these rises include so-called HIV treatment optimism, HIV serosorting, use of smart phone dating applications for meeting sexual partners, drug use ("chemsex"), HIV treatment as prevention, and preexposure prophylaxis (PrEP), which potentially contribute to increased sexual risk [2–5].

Primary syphilis is characterized by a lesion at the site of inoculation that, if untreated, may be followed by secondary syphilis. Early latent syphilis is defined as serological evidence of infection acquired within the previous 1 or 2 years (depending on country) in the absence of clinical manifestations. Untreated syphilis can lead to serious complications including ocular and neurosyphilis, increasing numbers of which have been reported and which have mainly occurred among MSM during early infection, including secondary syphilis [6–8]. Syphilis also increases the risk of HIV acquisition [9, 10] and increases HIV viral load in HIV-infected individuals [11].

Following a systematic review, the US Preventative Services Task Force recently concluded that there is evidence that syphilis screening of asymptomatic persons at increased risk for infection, including MSM, can provide substantial benefit [12]. Benefits of testing include prevention of onward transmission and the more serious manifestations of syphilis. Serological screening for syphilis is important as primary and secondary lesions in MSM can be overlooked by the individual or misdiagnosed by

Received 21 December 2016; editorial decision 20 February 2017; accepted 12 April 2017; published online April 13, 2017.

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Clinical Infectious Diseases® 2017;65(3):389–95

DOI: 10.1093/cid/cix326

healthcare providers, particularly when lesions are minor, atypical, or hidden, such as oral and anal lesions [13, 14]. Moreover, serological testing for syphilis is inexpensive, sensitive, and specific [12, 15]. Previous studies that demonstrated the benefits of syphilis screening of MSM have, however, been conducted at single clinics [16–19]. No previous studies have demonstrated the benefit of syphilis screening of MSM on a country level.

In Australia, the National Syphilis in Gay Men Action Plan was released in 2009 [20] and recommended frequent syphilis screening of higher-risk, HIV-negative MSM as well as opt-out serological screening for syphilis with routine HIV monitoring in HIV-positive MSM [20, 21]. Australian guidelines recommended that all MSM be screened for syphilis at least once a year, with more frequent screening of higher-risk men [21]. Our aim in this study was to examine trends in the rates of syphilis testing and diagnoses among MSM. Our objective was to determine whether increases in screening occurred and whether these were associated with greater detection of asymptomatic early syphilis at a country level.

METHODS

Study Population

The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) was established in 2007 as a national network of sentinel sites for sexually transmitted infection (STI) surveillance and is described elsewhere [22]. We examined data collected from 46 publicly funded sexual health clinics that participated in the ACCESS network between January 2007 and December 2014. Sexual health clinics within the network provided free STI and HIV testing to individuals who visited the clinics. Deidentified, line-listed data with a unique clinic identifier for each patient were extracted for those attending the clinics. Data included gender, date of clinic visit, gender of sexual partners, HIV status, serological testing for syphilis, diagnosis of infectious early syphilis (primary, secondary, or early latent), and HIV viral load testing for HIV-positive patients. Diagnoses of primary, secondary, and early latent syphilis (infection within 2 years) were made by clinicians at the clinics based on Australian Department of Health definitions [23]. Syphilis screening throughout the study period was based on *Treponema pallidum* immunoassays. If a patient had previously been treated for syphilis, a rise in rapid plasma reagin (RPR) titer was considered evidence of repeat infection. Australian guidelines recommended treatment of early syphilis with benzathine penicillin 1.8 g (2.4 million units) single dose by intramuscular injection.

Statistical Methods

All men who reported having sex with men at least once during the study period attending any of the ACCESS clinics during the study period were included in the analysis. The number of MSM attending the clinics and the number of clinic visits in each year were calculated. Data on serological testing for syphilis were used to calculate the proportion of MSM who were tested for syphilis at least once in a year (coverage) as well as the mean number of syphilis tests per man per year (frequency). The number of syphilis tests, diagnoses, and men were calculated for each calendar year. Linear regression was performed to determine whether the frequency of syphilis testing varied significantly over the study period. The number and proportion of early syphilis diagnoses by stage—primary, secondary, and early latent—was calculated by year. The χ^2 trend test was used to examine the proportion of syphilis cases by stage over time. The Mann-Whitney *U* test was used to examine the difference in age between HIV-positive and HIV-negative MSM. Pearson correlations were performed to examine the association between the proportion of syphilis diagnoses by stage and coverage of testing as well as frequency of testing by HIV status.

For HIV-positive MSM, the number of HIV viral load tests per year was ascertained as well as the proportion of these that were accompanied by syphilis testing on the same specimen. Syphilis testing of HIV-positive MSM not linked to HIV viral load testing was calculated separately. All statistical analyses were conducted using Stata, version 13 (StataCorp, College Station, Texas).

Ethical approval for the ACCESS project was obtained from the Human Research Ethics committees of Central Australia, St Vincent's Hospital Sydney, the Cairns Hinterland Health Service District, the Menzies School of Health Research, the South Metropolitan Area Health Service District, the Gold Coast Health Service District, the Alfred Hospital, Princess Alexandra Hospital, and Townsville Health Service District.

RESULTS

Number of MSM and Clinic Visits by HIV Status

A total of 359 313 clinic visits across the 46 network clinics between 2007 and 2014 were included in the analysis (Figure 1 and Supplementary Table 1). The number of individual HIV-negative MSM who attended the clinics each year increased from 7677 in 2007 to 19 179 in 2014, with a total of 246 041 clinic visits. The number of individual HIV-positive MSM who attended the clinics each year increased from 1664 in 2007 to 3273 in 2014, with a total of 113 272 clinic visits.

HIV-negative MSM (median age = 31 years; interquartile range [IQR] = 25–41) were younger than HIV-positive MSM (median age = 44 years; IQR = 36–52; $P < .0001$). The proportion of individuals identified as Aboriginal and/or Torres Strait Islander was higher among HIV-positive MSM (3.6%) compared to HIV-negative MSM (1.5%; $P < .0001$).

Syphilis Testing by HIV Status

HIV-negative MSM

Among HIV-negative MSM, the total number of syphilis tests performed each year increased from 4937 in 2007 to 27 187 in

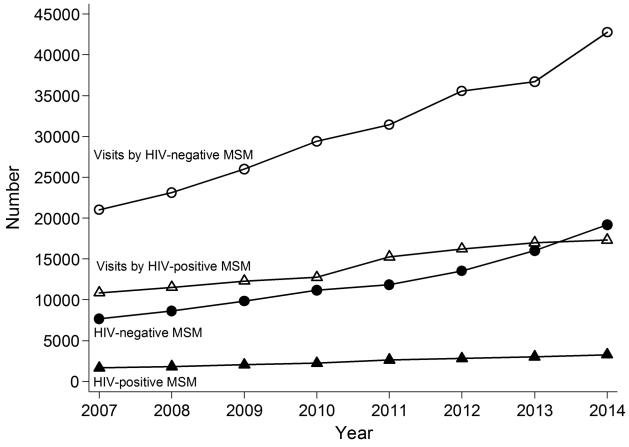

Figure 1. Annual number of men who have sex with men and clinic visits by human immunodeficiency virus status, 2007–2014. Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men.

2014 (Supplementary Table 1). The proportion of men tested at least once during a year, or test coverage, increased from 48% to 91% over the period ($P_{trend} < .0001$; Figure 2A). MSM aged ≤35 years had higher annual syphilis test coverage (50% in 2007 and 92% in 2014) compared to those aged >35 years (46% in 2007 and 89% in 2014; $P < .0001$). Among the 72 179 individuals who were tested for syphilis at least once in a year, the mean number of syphilis tests per man, or test frequency, increased modestly from 1.3 (standard deviation [SD] = 0.7) in 2007 to 1.6 (SD = 0.9) in 2014 ($P_{trend} < .0001$; Figure 3 and Supplementary Table 2). The mean time between syphilis tests over the period was 245 (SD = 286) days.

HIV-positive MSM

Among HIV-positive MSM, the total number of syphilis tests performed each year increased from 1148 in 2007 to 5667 in 2014 (Supplementary Table 1). The proportion of MSM tested at least once during that year increased from 42% to 77% over the period ($P_{trend} < .0001$; Figure 2B). MSM aged ≤35 years had higher annual syphilis test coverage (53% in 2007 and 87% in 2014) compared to those aged >35 years (39% in 2007 and 73% in 2014; $P < .0001$). Among the 12 368 individuals who were tested for syphilis at least once in a year, the mean number of syphilis tests per man increased to a greater extent than for HIV-negative MSM, from 1.6 (SD = 1.0) in 2007 to 2.3 (SD = 1.3) in 2014 ($P_{trend} < .0001$; Figure 3 and Supplementary Table 2). The mean time between syphilis tests over the period was 164 (SD = 188) days.

Among HIV-positive MSM, the number of HIV viral load tests performed each year increased from 3078 in 2007 to 6125 in 2014 (Figure 4 and Supplementary Table 3). The proportion of HIV viral load tests accompanied by a syphilis test on the same specimen increased from 27% in 2007 to 73% in 2014 ($P_{trend} < .0001$). In addition, syphilis tests were also performed in

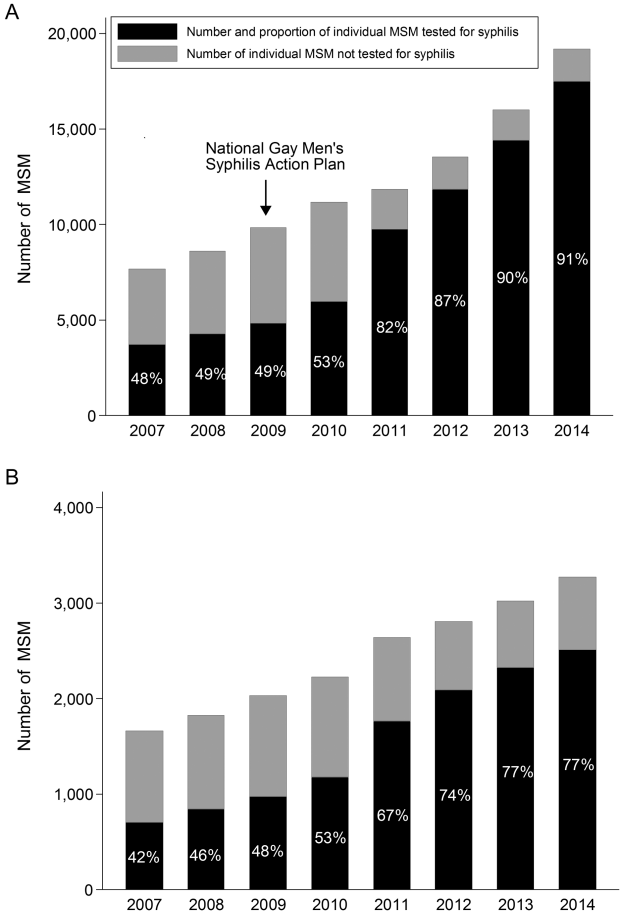

Figure 2. Annual number and proportion of men who have sex with men (MSM) tested for syphilis at least once in that year among (A) human immunodeficiency virus (HIV)–negative and (B) HIV-positive MSM, 2007–2014. Abbreviation: MSM, men who have sex with men.

HIV-positive MSM separate from HIV viral load testing. These increased from 308 to 1221 (Figure 4). The frequency of CD4 monitoring fell from a mean of 2.5 tests per year in 2007 to 2 tests per year in 2014.

Syphilis Diagnosis by Stage and HIV Status

HIV-negative MSM

Among HIV-negative MSM, there was an increase in the annual number of diagnoses of primary (117 to 225), secondary (59 to 113), and early latent (65 to 262) syphilis infections between 2007 and 2014 (Figure 5A and Supplementary Table 4). The proportion of early syphilis cases in HIV-negative MSM that were early latent infections increased from 27% to 44% ($P_{trend} < .0001$), while the proportion that were secondary infections decreased from 24% to 19% ($P_{trend} = .030$). The proportion of cases that were primary infections also decreased from 49% to 38% ($P_{trend} = .017$). Correlations between the proportion of syphilis cases diagnosed at each stage and testing coverage or frequency according to HIV status are shown in Supplementary Figures 1 and 2.

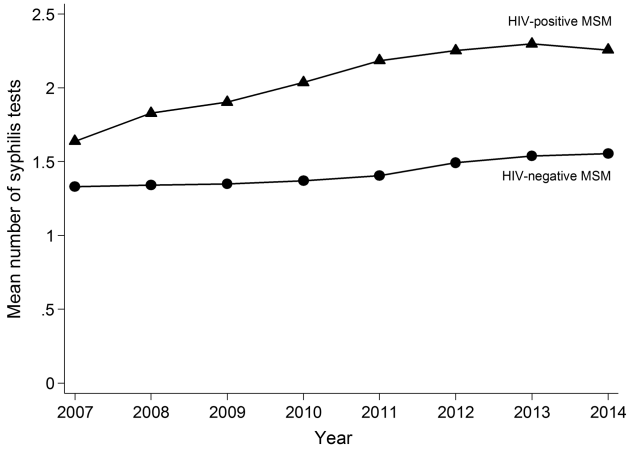

Figure 3. Mean number of syphilis tests per year per man by human immunodeficiency virus status, 2007–2014. Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men.

HIV-positive MSM

Among HIV-positive MSM, there was also an increase in the annual number of diagnoses of primary (30 to 67), secondary (41 to 60), and early latent (21 to 103) syphilis infections between 2007 and 2014 (Figure 5B and Supplementary Table 4). The proportion of early syphilis cases in HIV-positive MSM that were early latent infections increased from 23% to 45% ($P_{trend} < .0001$), while the proportion that were secondary infections decreased from 45% to 26% ($P_{trend} = .0003$). The proportion of cases that were primary infections remained relatively stable over the study period. Among HIV-positive MSM, there was a correlation between the decreasing proportion with secondary syphilis and increased testing coverage ($r = -0.87$; $P = .005$) and increased frequency of testing ($r = -0.93$; $P = .001$; Supplementary Figures 1 and 2).

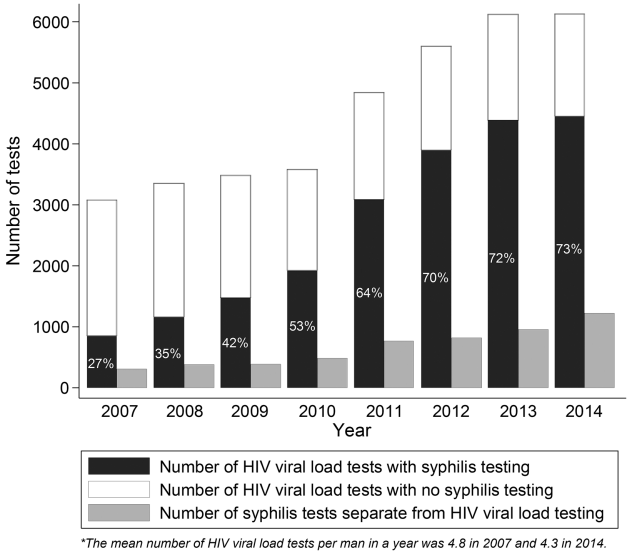

Figure 4. Annual number of human immunodeficiency virus (HIV) viral load tests in HIV-positive men who have sex with men and proportion accompanied by a syphilis test (see*). Abbreviation: HIV, human immunodeficiency virus.

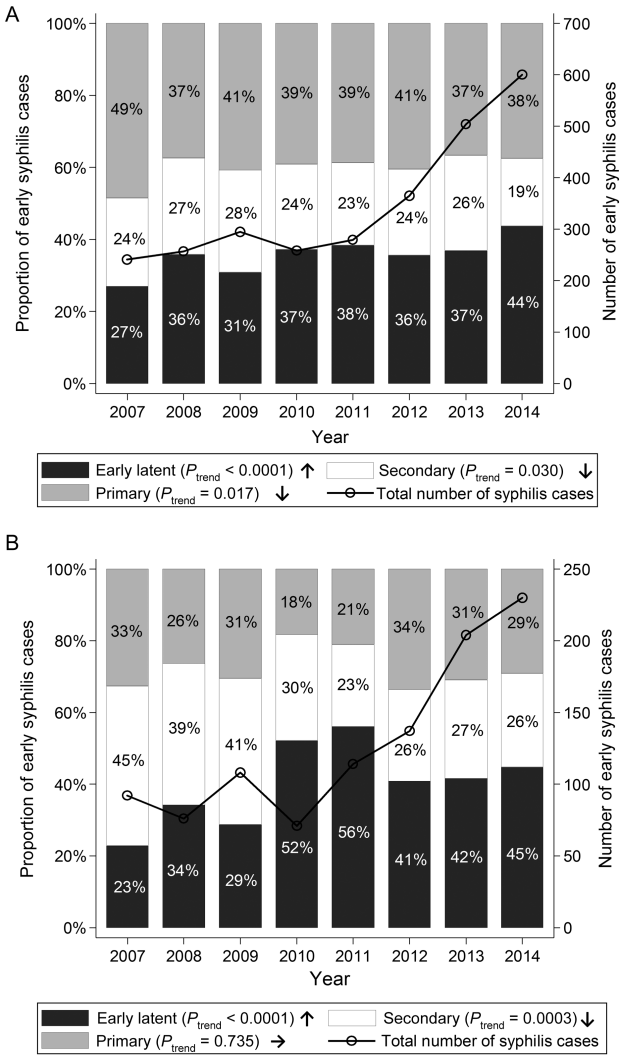

Figure 5. Annual number and proportion of early syphilis cases by stage in men who have sex with men (MSM), among (A) human immunodeficiency virus (HIV)–negative and (B) HIV-positive MSM, 2007–2014. *P* values for trend on the proportion of syphilis cases were calculated using χ^2 trend test. ↑ represents an increasing trend; ↓ represents a decreasing trend; → represents no significant trend was observed.

DISCUSSION

Through a national network of sentinel clinical sites, this study has shown that substantial increases in screening for syphilis were achieved among both HIV-positive and HIV-negative MSM across Australia. These increases were associated with an increase in the detection of early latent syphilis together with a relative decrease in secondary syphilis. Over the 8-year period, the proportion of early syphilis infections in HIV-negative MSM that were latent increased from 27% to 44%, while the proportion

that were secondary decreased from 24% to 19%. The proportion of early syphilis infections in HIV-positive MSM that were latent increased from 23% to 45%, while the proportion that were secondary decreased from 45% to 26%. Among HIV-positive MSM, there was a correlation between decreasing proportion of infections that were secondary and increasing testing coverage or frequency. We believe this is the first study to demonstrate that increased serological screening of MSM for syphilis is associated with greater detection of asymptomatic early syphilis, and with a measurable impact on secondary syphilis on a country level, providing evidence that screening is likely to have interrupted the progression of syphilis. This may have potentially reduced the infectiousness of syphilis, as it is believed the secondary stage of syphilis infection is particularly infectious [24], and prevented sequelae such as ocular and neurosyphilis [7, 8]. This occurred at a time of increasing notifications for syphilis among MSM in Australia and a likely increase in the underlying incidence of syphilis among MSM, which would explain the continued increase in total number of syphilis cases despite evidence for improved screening.

Over the study period, testing coverage among HIV-positive MSM was lower compared to HIV-negative MSM. The proportion of HIV-negative MSM who were tested at least once in a year for syphilis increased from 48% to 91%, while the increase in HIV-positive MSM was more modest, rising from 42% to 77%. The large increase in syphilis testing coverage among HIV-negative MSM likely reflects sustained efforts to promote HIV and syphilis testing of MSM, including those not previously tested for HIV, and improved access to sexual health clinics. The frequency of screening of individual MSM was higher and increased to a greater extent among HIV-positive MSM compared with HIV-negative men, averaging 2.3 tests vs 1.6 tests per man in 2014, respectively. The data suggest that the increase in frequency of screening of HIV-positive MSM reflected improved linkage of syphilis testing with HIV viral load testing, which rose markedly, from 27% to 73%.

Early latent infections may, in practice, represent diagnosis of asymptomatic infections that precede primary syphilis, occur between the primary and secondary stages, or follow secondary syphilis. The titer from nontreponemal testing generally increases at the beginning of the infection and falls over time without treatment; however, titers were not available from all network clinics. In a separate study from one of the largest clinics in the network conducted over a similar period, the median RPR titer for early latent syphilis was 1:32, between that for primary (1:4) and secondary syphilis (1:128) [25]. This observation supports our hypothesis that a substantial proportion of the early syphilis cases detected through the network may have been latent infections that preceded the secondary stage. Treatment of such cases would prevent progression to secondary syphilis and the morbidity that arises from this, explaining the decline in secondary cases. Detection and treatment of latent infections that follow the secondary stage would not have this effect, nonetheless, the duration of infectiousness would still be reduced.

A number of additional points should be considered when interpreting data from this study. First, the data on testing and diagnoses were from publicly funded sexual health clinics in Australia that prioritize STI and HIV testing of MSM and which have a high awareness of syphilis. The level of syphilis screening among MSM attending other health facilities is not known and may differ [26, 27]. Community-based surveys indicate that only 60% of Australian HIV-negative MSM report having had a syphilis test within the previous year [28, 29], suggesting a proportion of Australian MSM are not screened annually. If this is the case, this would have reduced the overall effectiveness of syphilis control among MSM in Australia. Second, we were not able to analyze data according to the level of sexual risk reported by men as behavioral data were not routinely collected at all clinics. Some MSM will have been at higher or lower risk for syphilis, and Australian guidelines recommend that MSM who have engaged in higher-risk practices have STI screening up to every 3 months, with annual screening of lower-risk men [21].

While syphilis testing coverage of HIV-positive MSM increased from 42% to 77% in 2014, 23% of men had not been tested in that year and 27% of HIV viral load tests were not accompanied by concurrent syphilis testing. Less syphilis testing of older MSM may to some extent have reflected exclusion of sexually inactive men, which may have included HIV-positive men attending clinics for HIV care. A previous study among HIV-positive MSM at one of the network clinics showed that inclusion of syphilis serology with blood tests routinely performed for HIV monitoring increased the proportion of early syphilis that was asymptomatic, from 21% to 85% [17]. The frequency of CD4 testing among HIV-positive MSM within the network fell over time, which is in line with less frequent monitoring for HIV in clinical practice [30, 31]. Further increases in the frequency of syphilis testing of HIV-positive MSM linked to routine CD4 or HIV viral load testing may be limited in clinics where syphilis testing is already high and may require that HIV-positive MSM are screened for syphilis separately, in addition to the blood tests obtained for HIV monitoring. The frequency of syphilis screening linked to HIV monitoring has varied between clinics in Australia, with those using an opt-out approach having a higher proportion of HIV-positive MSM screened for syphilis 3 times per year [26]. As HIV-positive MSM account for a disproportionate number of syphilis infections and repeat infections in many countries, further efforts and strategies to boost syphilis screening of HIV-positive MSM at health facilities where testing is suboptimal are warranted.

Although annual syphilis testing coverage of HIV-negative MSM attending clinics increased to 91% by 2014, the frequency of testing of individual MSM only increased modestly, from 1.3 to 1.6 tests per year, over the period. Novel interventions for

enhancing syphilis screening of MSM should be investigated; those shown to be effective should be implemented and integrated into clinic systems [32]. For example, an electronic health record alert was used at one network clinic to remind clinicians to advise high-risk MSM to receive frequent syphilis screening. This resulted in an increase in the proportion of syphilis that was asymptomatic, from 16% to 53% [16]. In another study at the same clinic, text message reminders were sent 3 monthly to MSM, reminding them to have STI screening. This was associated with greater detection of early asymptomatic syphilis [18].

The increases in syphilis cases in this study preceded the availability of PrEP for HIV in Australia. Studies suggest that the incidence of bacterial STI including syphilis among MSM using PrEP is likely to be high [4, 33]. It remains to be seen whether more widespread use of PrEP will further increase syphilis incidence and whether the STI screening that is recommended for individuals using PrEP will help limit the effect of any upward pressure on syphilis incidence. Ongoing surveillance is required to monitor trends in syphilis testing and syphilis incidence among MSM. Mathematical modeling studies to ascertain what level of screening would be sufficient to improve syphilis control among MSM would be of value. Further research on the cost effectiveness of syphilis screening of MSM would also be of benefit [34]. With reported rates of syphilis at historical highs in many countries, other potential measures aimed at syphilis control such as vaccine development [35], chemoprophylaxis [36], and community-based screening require further investigation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. P. F. C. and M. Y. C. conceived the study design and wrote the first draft of the manuscript. E. P. F. C. performed data analyses and data interpretation. R. G., B. D., and M. H. established the ACCESS collaboration. D. C. managed the data collected from the ACCESS sexual health network and assisted with data analyses. All authors helped with interpretation of data, manuscript editing, and approval of the final version.

Acknowledgments. We thank all sentinel sites that provided data for ACCESS.

Financial support. E. P. F. C. is supported by a National Health and Medical Research Council Early Career Fellowship (1091226). The ACCESS collaboration was funded by the health departments of the Australian Capital Territory, the Northern Territory, New South Wales, and Victoria. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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