

ORIGINAL ARTICLE

Can enhanced screening of men with a history of prior syphilis infection stem the epidemic in men who have sex with men? A mathematical modelling study

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ABSTRACT

Objectives The aim of this study is to determine the transmission impact of using prior syphilis infection to guide a focused syphilis screening intervention among men who have sex with men (MSM).

Methods We parameterised a deterministic model of syphilis transmission in MSM to reflect the 2011–2015 syphilis outbreak in Winnipeg, Canada. Enhanced screening of 75% of men with prior syphilis every 3 months (A) was compared with distributing equivalent number tests to all MSM (B) or those with the highest partner number (C). We compared early syphilis incidence, diagnoses and prevalence after 10 years, relative to a base case of 30% of MSM screened annually.

Results Strategy A was expected to avert 52% of incident infections, 44% of diagnosed cases and reduce early syphilis prevalence by 89%. Strategy B had the least impact. Strategy C was most effective, averting 59% of incident cases. When screening frequency was semiannual or annual, strategy A was the most effective.

Conclusions Enhanced screening of MSM with prior syphilis may efficiently reduce transmission, especially when identification of high-risk men via self-reported partner numbers or high-frequency screening is difficult to achieve.

INTRODUCTION

Frequent syphilis screening remains the best available biomedical tool for syphilis control. Mathematical modelling studies suggest that frequent (every 3–4 months) screening may be an effective and cost-effective approach to syphilis control among populations with high syphilis incidence.^{1–4} However, considerable resources are often required to achieve high-frequency screening of all at-risk individuals,⁵ and increased screening may lead to a paradoxical increase in cases⁶ or resurgence following apparent control if screening cannot be sustained.⁷ Implementable approaches to focus screening to those most at risk are needed to maximise impact in an efficient and sustained manner.

Focusing on individuals who are disproportionately vulnerable to acquisition and transmission of infection (core groups) remains a strategic focus for STI control. However, identifying core group members may be challenging, with STI screening guidelines often using self-reported behaviours to

identify individuals at greatest risk for STI acquisition. The Canadian city of Winnipeg recently initiated a novel approach for increasing screening in at-risk individuals. Under this programme, all individuals diagnosed with syphilis are offered the option to receive testing reminders every 3 months. As of May 2017, greater than 80% of individuals diagnosed with syphilis had agreed to participate. The rationale for focusing on those with a prior infection relates to the observation that individuals with a prior syphilis infection experience an increased future risk of syphilis and other STIs.⁸ Importantly, a prior infection may signal ongoing vulnerability to STI acquisition and transmission due to sexual network factors, independent of self-reported sexual behaviours such as number of sexual partners.^{9–14} The extent to which a prior syphilis infection could help identify core group members without requiring elicitation of sexual behaviours has not been examined.

In parallel with the implementation of this new strategy in Winnipeg, we used mathematical modelling to examine the potential effectiveness of using previous infection as a marker of risk in a focused screening intervention and compared its impact on reducing syphilis burden with that of other screening strategies—universal screening or focused screening based on number of sexual partners. Our model specifically focused on men who have sex with men (MSM), who experience elevated rates of infection and was informed by data from the ongoing syphilis epidemic in Winnipeg.

METHODS

Model overview

We modified a previously described deterministic compartmental model of syphilis transmission in MSM⁶ to capture the demographic and epidemiological features of the 2011–2015 outbreak in Winnipeg, Manitoba. Table 1 presents the model parameters, which were drawn from the biomedical literature, where possible, or by assumption or model calibration otherwise. Model equations and additional details are provided in online supplementary file 1.

The natural history of syphilis infection was modelled by including the following states: susceptible, incubating, primary, secondary, early latent and late latent infection (see online supplementary

Table 1 Model parameter values

Parameter	Symbol	Value	Range	Source
Average time in model (years)	$1/\mu$	20		Assumption
Transmission probability per sexual partnership	β	0.6		Garnett <i>et al</i> ¹⁶
Average duration of syphilis stage (months)				Garnett <i>et al</i> ¹⁶
Incubating	$1/\delta$	0.9		
Primary	$1/\gamma_1$	1.5		
Secondary	$1/\gamma_2$	3.6		
Early latent	$1/\gamma_3$	6.9		
Background antibiotic treatment rate (per year)	p_{abx}	0.01		Assumption
Time in treated (and immune to reinfection) state				Garnett <i>et al</i> ¹⁶ ; assumption
Primary and secondary	$1/\lambda_1$	1 week		
Early latent	$1/\lambda_2$	1 week		
Late latent	$1/\lambda_3$	5 years	1 week to 5 years	
Proportion of population in sexual activity group	N_i			PHAC ¹⁹
Low		0.3		
Moderate		0.5		
High		0.2		
Relative rate of partner acquisition per year (by activity group)	rp_i			PHAC ¹⁹ ; assumption
Low		1		
Moderate		5		
High		20		
Rate of partner acquisition in low activity group (per year)	c_{min}	0.40	0.33–0.40	Calibration
Mixing between sexual activity groups	ϵ	0.48	0.48–0.95	Calibration
Proportion of population screened for syphilis (base case)	Coverage	0.3		PHAC ¹⁹ ; assumption
Screening interval (years)	Interval	1	0.25–1	Assumption
Probability of actively seeking medical care for infection				Calibration
Primary	p_{tr1}	0.25		
Secondary	p_{tr2}	0.30		
Early latent	p_{tr3}	0.25		

PHAC, Public Health Agency of Canada.

figure 1). Transmission occurred through sexual contact between susceptible and infectious individuals. The primary and secondary stages were assumed to be infectious. In the absence of treatment, infected individuals progressed through the various stages of infection and remained in the late latent stage until they exited the modelled system. We assumed that untreated individuals with syphilis could not be infected with another strain (ie, no superinfection). Men treated for early (primary, secondary or early latent) infection were assumed to be protected from reinfection for 1 week following treatment, reflecting the persistence of penicillin in the body following administration.¹⁵ Treatment of late syphilis was followed by an average of 5 years of immunity from reinfection.^{16 17}

The model population was separated by previous infection status: men with a reported syphilis infection entered a ‘susceptible, previously treated’ compartment (S_R) following treatment. The natural history was identical for first and repeat infections. We included a ‘susceptible, treated but unreported’ compartment (S_{ABX}) to distinguish men with treated syphilis whose initial infection was not reported in the local public health system. This might occur due to inadvertent treatment of syphilis from background antibiotic use for non-syphilis indications or treatment in another public health jurisdiction. Such cases are not flagged as individuals with a history of infection but must be considered when calibrating the model to seroprevalence estimates based on serology which remains positive after treatment.¹⁸ If infected again, men with ‘treated but unreported’ syphilis transitioned through the

same compartments as infection-naïve individuals. Following a reported syphilis infection, men entered and remained in ‘previously treated’ part of the model.

The model included three levels of sexual activity (high, moderate and low), with the proportions of sexually active men in each category based on self-reported partner numbers in the most recent (2006) biobehavioural survey of a convenience sample of 121 Winnipeg MSM.¹⁹ The high-activity group comprised 20% of MSM with rates of partner change 20-fold higher than rates in the low-activity group. Mixing between sexual activity groups could range from proportionate (no preferential partnerships between groups, $\epsilon=0$) to assortative ($\epsilon=1$, where individuals partner exclusively with individuals of the same risk group). ϵ was estimated by model calibration. Additional details on the calculation of force of infection by sexual activity are provided in the technical appendix (see online Supplementary file 1). Men remained in the model for 20 years on average. The modelled population size remained constant and individuals did not move between activity groups.

Screening and treatment

Syphilis was diagnosed and treated if individuals with infection actively sought medical care for symptoms, through partner notification or by participating in opportunistic screening for asymptomatic syphilis. For individuals actively seeking care, treatment was assumed to occur at the midpoint of the infection stage.

We assumed a constant hazard of screening (α), with the probability of screening converted to a rate, assuming an exponential distribution²⁰:

$$-\ln(1 - \text{coverage}) / \text{screening interval}$$

where the coverage reflected the proportion of the population screened in each screening interval (base case, 1 year).²¹ For simplicity, we assumed 100% sensitivity and specificity of the diagnostic tests and 100% treatment efficacy.

Model calibration

We used Winnipeg early syphilis case data from 2011 to 2015 for model fitting. Over the 5-year period, there were 171 early syphilis cases in men reporting sex with male partners (bisexual and MSM), accounting for 80% of early syphilis cases among all male cases reported in Winnipeg. Rates in MSM were estimated to range from a minimum of 140 per 100 000 in 2011 to a maximum of 996 per 100 000 in 2014. Of early syphilis cases, 7.7% were repeat infections. Additional details on model fitting and estimation of the size of the Winnipeg MSM population are provided in online supplementary file 1.

Interventions

After the calibration period, we projected the potential impact of different screening interventions applied to the modelled population over a 10-year time period (see online supplementary table 1). Men with a syphilis diagnosis up to 5 years prior to the start of the intervention were included in the previously infected stratum of the model to correspond with the cut-off used in the actual Winnipeg intervention. Our base case scenario was 30% screening of the entire modelled population of MSM annually, and we compared this to the following enhanced screening interventions, with an equivalent volume of additional tests used for each strategy. For each of these strategies, we assumed that 30% screening of the entire population continued, with additional screening tests distributed as follows:

- ▶ Focused screening every 3 months of men with prior reported syphilis infections
- ▶ Uniform screening every 3 months (ie, uniform distribution of additional tests)
- ▶ Focused screening every 3 months of men in the high sexual activity group

In strategy A, 75% of men with a prior reported infection were screened every 3 months. The additional number of tests under strategy A varied over time because the number of men with prior syphilis infection changed over the course of the epidemic. Therefore, we calculated the number of additional tests performed each year under strategy A compared with the base case (constant 30% annual screening across the intervention period) and redistributed these additional tests across the entire MSM population (strategy B) or to men with the highest number of partners (strategy C), with this extra screening occurring every 3 months. In every scenario, 30% of the MSM population not reached by the additional volume of tests continued to receive annual screening.

Outcomes included the following relative changes over a 10-year time horizon compared with the base-case: (1) cumulative diagnosed cases of early syphilis; (2) cumulative incidence of syphilis and (3) early syphilis prevalence at the end of the intervention period.

Sensitivity analyses: natural history and intervention assumptions

We conducted three sensitivity analyses. First, to explore the influence of screening intensity on outcomes, we repeated the comparative analysis assuming annual or semiannual screening frequencies. Second, we explored the influence of scaling down the enhanced screening programme in strategy A after 2 years of implementation. The scale down involved three possibilities: screening in men with prior infection was reduced in frequency from every 3 months to (1) semiannually or (2) annually, with coverage maintained at 75%, or (3) all screening returned to baseline (30% MSM receiving annual screening).

Third, due to uncertainty surrounding the existence and duration of protective immunity following treatment of late syphilis,^{16 17} we recalibrated the model and repeated our analyses under the assumption that men treated for late latent infection became susceptible after 1 week or 1 year.

Ethics approval

Research ethics board approval was not required because syphilis surveillance data from the Winnipeg Regional Health Authority were provided to the research team as aggregate data, with no personal identifying information.

RESULTS

Model calibration

The model reproduced the overall trend of increasing early syphilis diagnoses in MSM in Winnipeg (see online supplementary figure 2). Estimated syphilis seroprevalence at the end of the calibration period matched survey data¹⁹ at 3.3%. At the end of the calibration period, 5.6% of annual diagnosed early syphilis cases were repeat infections (ie, occurred in men with a recognised previous infection).

Base case scenario

Under base case assumptions, prevalence and incidence were projected to decline over the intervention period (figure 1). Reinfections accounted for 16% of diagnosed early syphilis infections and 14% of all incident infections by the end of the 10-year intervention period, when early syphilis prevalence was projected to be 4 per 1000 MSM.

Enhanced screening strategies

In all intervention scenarios, we projected an initial transient increase in diagnosed early syphilis cases (figure 1) relative to the base case. The increase was largest under strategy C, which was focused on increasing testing among men with the highest number of partners.

Compared with the base case, enhanced screening of men with prior diagnosed syphilis (strategy A) was projected to reduce the prevalence of early syphilis by an additional 89% at the end of the intervention period. This strategy was expected to avert 52% of incident infections and 44% of diagnosed cases relative to the base case.

Uniform enhanced screening (strategy B) was expected to have less of an impact than focused screening, reducing prevalence by 39% and averting 19% of incident and 14% of diagnosed cases. Focused screening of men with a high number of partners (strategy C) was projected to be the most effective strategy, averting 59% of incident cases and reducing prevalence by 95% relative to the base case.

Of the interventions evaluated, focused screening in men with a prior infection had the greatest impact on reducing

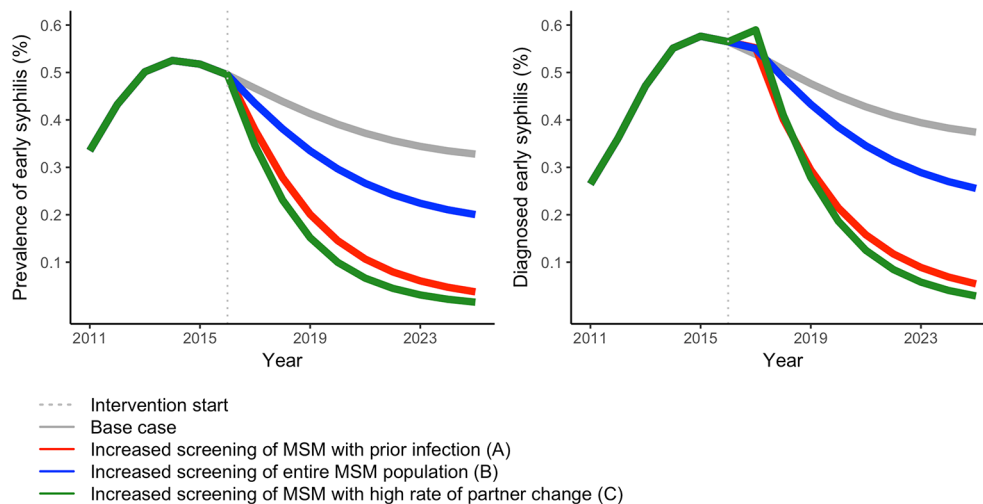


Figure 1 Model projections of syphilis prevalence and diagnosed cases over a 10-year intervention period. The dashed lined indicates the start of the intervention period. The base case assumed 30% population screening annually (applied uniformly across the population). The 'prior infection' scenario (A) involved 75% of the population with a recognised prior syphilis infection being screened every 3 months. The 'entire population' (B) and 'high rate of partner change' (C) scenarios involved distributing an equivalent number of tests to those used in scenario A to either the general population or men with the highest rates of partner change every 3 months. MSM, men who have sex with men.

syphilis prevalence syphilis in this group (see online supplementary figure 3). Screening men with high rates of partner change also reduced prevalence among men with a prior infection, but to a lesser degree. At the end of the intervention period, the majority of prevalent early syphilis cases were in men with the highest rate of partner change, regardless of the screening strategy used. Strategy C was the most effective for

reducing the relative infection burden in this group (see online supplementary figure 4).

Sensitivity analyses

When frequency of enhanced screening was reduced to semi-annually or annually, focusing on men with prior infection was

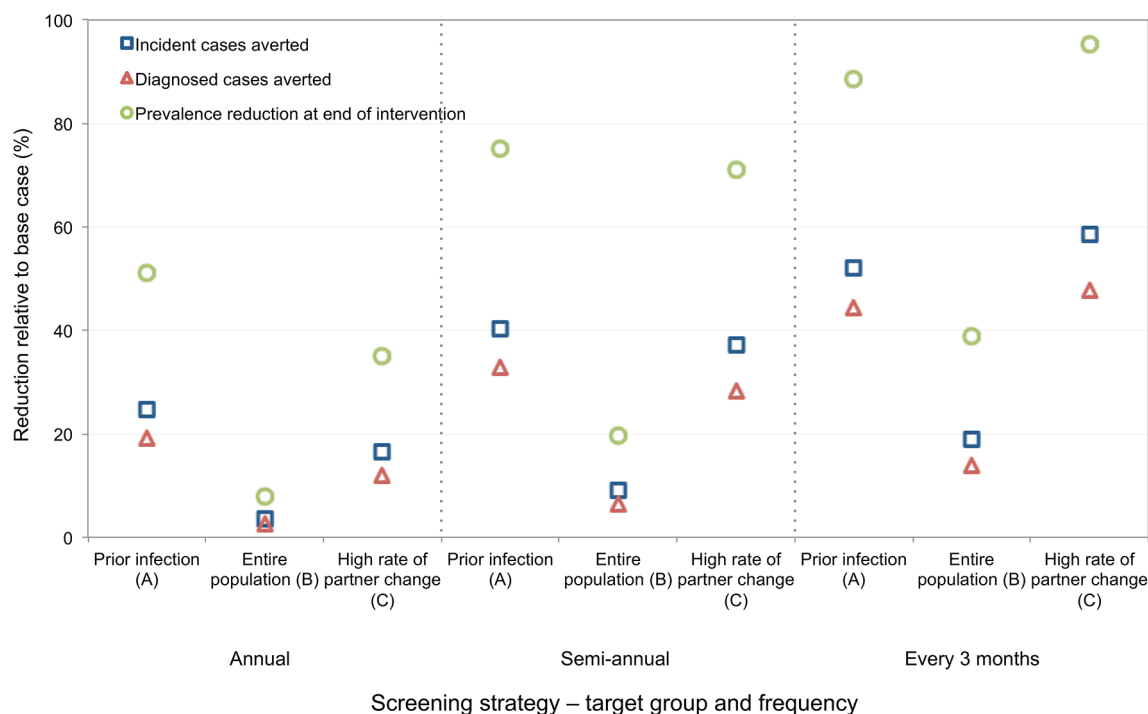


Figure 2 Impact of different screening frequencies on intervention effectiveness. The proportionate reduction in incident cases, diagnosed cases and prevalence at the end of the intervention period was determined relative to the base case scenario (30% annual population screening). Results are shown for different frequencies of screening. For the prior infection strategy (A), 75% of the eligible population was screened at the indicated frequency, with the required test numbers for the entire population (B) and high rate of partner change (C) strategies calculated based on the number of men with previous infection at the start of each intervention year.

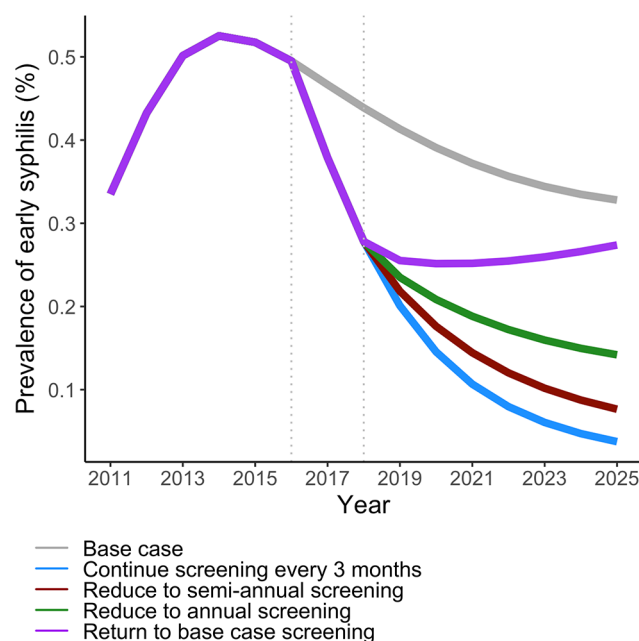


Figure 3 Impact of reducing intervention intensity over time. We evaluated the impact of reducing the frequency or coverage of screening in MSM with a prior syphilis infection on prevalence of early syphilis. The first vertical line indicates the start of the intervention period, while the second dashed line indicates the time at which intervention intensity could be reduced. At the start of the intervention, 75% of men with a prior infection were screened every 3 months. After 2 years, this could be maintained (blue), reduced to 75% of men with prior infection screened every 6 months (red), reduced to 75% of men with prior infection screened annually (green) or reduced to 30% of men (regardless of prior infection history) screened annually (purple). The base case of 30% of MSM screened annually (grey) is shown for comparison.

equally or more effective than allocating tests to men with high rates of partner change (figure 2).

Scaling down the intensity of strategy A after 2 years reduced its overall impact, compared with what was observed when enhanced screening was sustained, but the prevalence of early syphilis still remained lower than the base case (figure 3). Notably, if screening returned to baseline levels after 2 years of enhanced screening, syphilis prevalence was projected to rebound during the 10-year evaluation period.

Reducing the duration of protective immunity following treatment for late latent syphilis produced fewer oscillations in prevalence in base case projections (see online supplementary figure 5). Nonetheless, the relative differences in outcomes across screening strategies remained consistent across assumptions about duration of protective immunity.

DISCUSSION

Using a model of syphilis transmission that explicitly captures reinfection, we compared three strategies to enhance screening and interrupt transmission among MSM. We found that for an equivalent number of additional tests, focused screening was more effective than universal screening. Prioritised screening of MSM with a history of syphilis was potentially the most effective strategy when high-frequency (every 3 months) screening could not be achieved, and provides an alternate approach to self-reported sexual behaviour for identifying those most at risk of infection. Short-term, high-frequency screening of MSM with prior syphilis was projected to produce large and

sustained reductions in syphilis cases even if screening intensity is scaled back after 2 years, but screening must remain higher than baseline to avoid a resurgence of cases in the medium term.

After treatment for early syphilis, standard of care includes repeat serology at 3, 6 and 12 months and 24 months. The enhanced screening approach would involve one additional test in the first year post treatment (ie, at 9 months after treatment) and 3–4 additional tests per year thereafter. Few settings in practice achieve screening intervals of 3 months with high coverage. Barriers to increasing the frequency of screening to all or even a subset of MSM include: requiring that individuals return to clinics for syphilis (and other STI) screening in the absence of any other healthcare needs and resource limits on clinic and outreach capacity. Several settings have attempted routinised syphilis testing to increase frequency, employing measures such as computerised reminders or ‘opt-out’ syphilis tests with routine HIV viral load tests among persons living with HIV.^{5 22–24} Our model projected that if enhanced screening frequency was semi-annual or annual, then prioritising those with a prior syphilis history was the most effective strategy.

Enhanced screening may lead to an initial rise in diagnosed (as opposed to incident) cases. For all of the intervention strategies we evaluated, there was an approximately 2-year period when diagnosed cases would be higher than baseline while ‘true’ underlying prevalence fell. The observation is an artefact of disease surveillance: as screening is intensified among those at risk, we find and treat more cases. Thus, an initial increase in diagnosed cases may be a sign that screening programmes are having the desired effect and should not be interpreted by surveillance as an increase in incidence or prevalence. Misinterpretation of such trends can lead to concerns that enhanced screening is ineffective and further stigmatise communities vulnerable to STIs. While this issue could be addressed by adjusting incidence for testing denominators, in practice such denominator data are seldom available for communicable diseases of public health importance.²⁵

To our knowledge, this is the first modelling study to explore the impact of enhanced screening in individuals with a history of prior infection. Strengths of the study include the inclusion of a history of prior syphilis infection and the fact that it was informed by the best available local data on the epidemiological characteristics of the Winnipeg syphilis epidemic. There are important limitations to the study. The regional, sexual behavioural parameters were collected over 10 years and from a small sample size; the limitations of these inputs were offset by calibrating the input parameters to observed rates of syphilis infections over time. Our results are conditional on the epidemiological context under study, and the relative impact of focused screening of MSM with prior syphilis may vary by the rates of reinfection in the region of interest. Relatedly, the syphilis epidemic in Winnipeg has evolved, making significant inroads into heterosexual populations²⁶; further research is needed to understand the impact of focused screening of populations susceptible to reinfection on mixed or parallel syphilis epidemics.

Nonetheless, this study provides insights that can lead directly to pragmatic programme change, as public health authorities often do have case history data that would identify individuals as having prior syphilis infection, whereas the validity of self-reported sexual behaviour data appears to vary widely across populations.²⁷

Simpler, less subjective, risk markers could allow for a more efficient use of screening resources than behavioural screening. Identifying those at highest risk of syphilis acquisition based on self-reported behaviour requires that providers ask the pertinent

questions and risk-stratify patients accordingly that patients disclose details of sexual partnerships and their sexual orientation to providers and that both sides engage in a discourse surrounding sexual health. In one study, less than half of MSM report talking to their primary care provider about sexual health,²⁸ while another study found those who had not disclosed to their providers were less likely to receive HIV/STI testing.²⁹ Behavioural screening for syphilis screening also places the burden of decision making and the delivery of a public health strategy on individual patient-provider interactions. Furthermore, individuals classified as 'low risk' by behavioural surveillance may have a small number of sexual partners within a sexual network with high-syphilis prevalence that places them at high risk of acquisition and repeat infection. Using a clinical history of syphilis infection as the risk marker means that public health teams can deliver the screening strategy and support providers accordingly. In this study, we found that even in the face of perfect information on sexual behaviour, screening strategies based on prior syphilis infection history either approached or outperformed behaviour-based strategies. The insights generated by this model provide helpful and practical guidance to public health practitioners and decision makers working to control syphilis resurgence.

Key messages

- Modelling studies suggest that frequent screening can reduce syphilis burden, but high-frequency screening has been challenging to achieve in practice.
- We investigated if prior infection history could be used to focus limited public health resources to those most likely to benefit from regular syphilis screening.
- We used a mathematical model to compare enhanced screening in MSM with a prior infection to standard screening approaches.
- Even in the face of perfect information on sexual behaviour, screening strategies based on prior syphilis infection history either approached or outperformed behaviour-based strategies.

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Contributors All authors participated in study conception and design and interpretation of results. AT built the model and performed the analyses. SS, JR and CR assisted with data acquisition. AT and SM drafted the manuscript, and all authors assisted with critical revision of the manuscript.

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Data sharing statement Model code is available upon request by contacting the corresponding author.

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