The cost-effectiveness of syphilis screening among men who have sex with men: An exploratory modeling analysis

Technical appendix

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Revised March 22, 2016
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1 The model

The population of men who have sex with men (MSM) aged 15 to 64 years was divided into four health states, S, Š, I, and Ŧ, where S denotes those susceptible to *Treponema pallidum* and I denotes those infected with *Treponema pallidum*, and the “hat” (^) indicates those with HIV:

\[ S = \text{Number of MSM without syphilis, without HIV}; \]
\[ Š = \text{Number of MSM without syphilis, with HIV}; \]
\[ I = \text{Number of MSM with syphilis, without HIV}; \]
\[ Ŧ = \text{Number of MSM with syphilis, with HIV}. \]

Transition from one health state to another from week t to week t + 1 was calculated using the following difference equations:

\[ S_{t+1} = S_t - S_t \lambda_{HIV} \Omega_{HIV} \Phi_{HIV} - S_t \lambda_{STD} \Omega_{STD} + I_t r, \]
\[ I_{t+1} = I_t - I_t r - I_t \theta \lambda_{HIV} \Omega_{HIV} \Phi_{HIV} + S_t \lambda_{STD} \Omega_{STD}, \]
\[ Š_{t+1} = Š_t - Š_t \lambda_{STD} \Omega_{STD} + S_t \lambda_{HIV} \Omega_{HIV} \Phi_{HIV} + Ŧ_t r, \]
\[ Ŧ_{t+1} = Ŧ_t - Ŧ_t r + I_t \theta \lambda_{HIV} \Omega_{HIV} \Phi_{HIV} + Š_t \lambda_{STD} \Omega_{STD}, \]

where \( \lambda_{HIV} \) denotes HIV incidence at the onset of the syphilis screening program among those without syphilis; \( \lambda_{STD} \) and \( \lambda_{STD} \) denote syphilis incidence rates at the onset of the syphilis screening program among those without and with HIV, respectively; \( \Omega_{HIV} \) and \( \Omega_{STD} \) are adjustment factors to account for dynamic changes in HIV and syphilis prevalence over time; \( \Phi_{HIV} \) is an adjustment factor to account for the facilitative effects of syphilis on HIV transmission (\( \Phi_{HIV} \) changes over time to account for changes in HIV/syphilis co-infection in the population over time), \( \theta \) represents the relative rate of HIV incidence among those with syphilis (vs. those without syphilis) due to the facilitative effects of syphilis on HIV acquisition; and r and Ŧ represent the recovery rate of syphilis among those without and with HIV, respectively.
See Appendix Table 1 for a description of each of the symbols used in the above equations. More complete details of the model are provided below and in Appendix Tables 1 and 2.

2 Overview of model

2.1 Closed population

The modeled population consists of MSM aged 15 to 64 years. In all of the results we present in the manuscript, there was no entry or exit from the population over the 10-year period (a closed population). In previous analyses with a similar model, the cost-effectiveness of screening MSM for rectal gonorrhea was slightly more favorable when the model allowed entry and exit from the population (vs. a closed population).1

2.2 Weekly calculations

The model’s time cycles were one week in length, and the impact of syphilis screening was modeled over 10 years (520 cycles). Weeks are denoted by \( t \); thus the equations above describe how the distribution across the four health states changes from one week to the next. Annual probabilities and annual rates presented in the manuscript and in this appendix were converted to weekly rates as shown in Appendix Table 2.

2.3 Stratification of population

Our model inputs reflect averages for all MSM aged 15 to 64 years, stratified only by HIV status and syphilis status. We used average HIV incidence rates and average syphilis incidence rates, and did not classify MSM according to their sex practices (e.g., receptive only, insertive only, both, or neither), number of new sex partners per year, age, or any other factor.

Syphilis status was categorized as those with syphilis and those without syphilis, without regard to stage of syphilis, such as primary and secondary (P&S) syphilis, early latent syphilis, late and late latent syphilis. We assumed that the facilitative effects of syphilis on HIV transmission and acquisition would occur primarily in the P&S stage. However, rather than modeling the stages of syphilis, we simply adjusted the syphilis cofactor effects on HIV acquisition and transmission to account for the average time spent in the P&S stage as a percent of the average duration of infection, as described in more detail below.
2.4 Simplified transmission dynamics

We did not explicitly model the mixing of sex partners and the per-act or per-partnership probability of syphilis transmission. Instead, we applied literature-based estimates of syphilis incidence rates among MSM with and without HIV. These syphilis incidence rates were multiplied by an adjustment factor ($\Omega_{\text{STD}}$) to account for changes in the prevalence of syphilis in sex partners over time as a result of the syphilis screening program.

Likewise, we did not explicitly model the mixing of sex partners and the per-act or per-partnership probability of HIV transmission. Instead, we applied literature-based estimates of HIV incidence rates among MSM. These HIV incidence rates were multiplied by an adjustment factor ($\Omega_{\text{HIV}}$) to account for changes in the prevalence of HIV in sex partners over time as a result of the syphilis screening program.

2.5 Syphilis cofactor effects on HIV acquisition and transmission

We assumed that syphilis would increase susceptibility to HIV, such that HIV incidence rates would be higher among MSM with syphilis than among MSM without syphilis. The rate of HIV incidence among those with syphilis was assumed to be $\theta$ times that of those without syphilis.

We assumed also that syphilis would enhance HIV transmission. We used the adjustment factor $\Phi_{\text{HIV}}$ to account for the facilitative effects of syphilis on HIV transmission. The adjustment factor $\Phi_{\text{HIV}}$ was a function of $\delta$, the cofactor effect of syphilis on HIV transmission. That is, we assumed the probability of HIV transmission from a person with HIV and syphilis would be $\delta$ times that of a person with HIV but without syphilis.

2.6 Dynamic and static versions of the model

We estimated two model versions; a static version and a dynamic version. The static version included benefits of syphilis screening only to those who are screened, whereas the dynamic version used the simplified approach described above to approximate the population-level benefits of syphilis screening. In the dynamic version, the adjustment factors ($\Omega_{\text{STD}}$ and $\Omega_{\text{HIV}}$) were used to account for changes in the prevalence of syphilis and HIV, respectively, in sex partners over time as a result of syphilis screening, and the adjustment factor $\Phi_{\text{HIV}}$ was used to account for changes in syphilis/HIV
coinfection under the assumption that syphilis coinfection increases HIV infectivity. In the static version of the model, all three of these adjustment terms were set to 1.

3 Details of model parameters

3.1 Syphilis incidence rates among MSM with and without HIV

The annual syphilis incidence rate among MSM aged 15 to 64 years was based on 17,967 reported P&S cases in men aged 15 to 64 years in 2014, of which 83.1% were assumed to be in MSM (CDC surveillance data). These 14,931 cases (17,967 x 0.831) were multiplied by 3.6 to account for under-reporting. The population size of MSM for the denominator (4.09 million) was calculated assuming 3.9% of men are MSM. Syphilis incidence rates for MSM with and without HIV were calculated assuming 20% HIV prevalence among MSM and that MSM with HIV account for 50% of MSM syphilis cases. These assumptions yielded annual syphilis incidence rates of 3,290 per 100,000 MSM with HIV and 820 per 100,000 MSM without HIV. Lower and upper bound values for the syphilis incidence rate were calculated by varying the under-reporting adjustment factor from 2 to 5.

3.2 HIV incidence rates among MSM with and without syphilis

Annual HIV incidence among MSM without syphilis ($\lambda_{HIV}$) was assumed to be 0.016, calculated as the average of two estimates of HIV incidence rate among MSM overall: 2.25% from a literature review and 0.9% based on the estimated 29,800 new cases of HIV in men acquired from male-to-male sexual contact in 2010 combined with the MSM population and HIV prevalence assumptions noted above.

As described below, we assumed a cofactor effect of syphilis on HIV acquisition of 1.3 and an average duration of syphilis of 123 weeks in the absence of syphilis screening. Our assumption of annual syphilis incidence of 820 per 100,000 and a 123 week average duration yielded syphilis prevalence rates of about 1.9% among MSM without HIV. Under these assumptions, $0.016 = 0.019*1.3 \lambda_{HIV} + 0.981* \lambda_{HIV}$, where $\lambda_{HIV}$ is HIV incidence among MSM without syphilis. Solving for $\lambda_{HIV}$ yielded an annual HIV incidence rate of 1.6% for MSM without syphilis (which, due to rounding, does not differ from the 1.6% estimate of HIV incidence among MSM overall). Lower and upper bound values for the HIV incidence rate among those without syphilis were calculated as 50% and 150% of the base case value.
HIV incidence among those with syphilis was calculated as the product of the HIV incidence rate among those without syphilis ($\lambda_{HIV}$) and the syphilis cofactor effect on HIV acquisition ($\theta = 1.3$), which in the base case was calculated as $\theta \lambda_{HIV} = 1.3 \times 0.016 = 0.021$.

### 3.3 Transmission dynamic adjustment factors ($\Omega_{STD}$ and $\Omega_{HIV}$)

#### 3.3.1 Syphilis transmission dynamics

To incorporate transmission dynamics in our model, the rate of acquisition of syphilis was multiplied by an adjustment factor ($\Omega_{STD}$) to account for changes in the prevalence of syphilis in the MSM population over time. This adjustment factor ($\Omega_{STD}$) in week $t+1$ was calculated based on the ratio $\psi_{t+1} = (\text{STD}_\text{Screen}_t / \text{STD}_\text{NoScreen}_t)$, where $\text{STD}_\text{Screen}_t$ is syphilis prevalence at week $t$ in the scenario of syphilis screening and $\text{STD}_\text{NoScreen}_t$ is syphilis prevalence at week $t$ in the scenario of no syphilis screening. For example, if syphilis prevalence in the scenario of syphilis screening was 5% lower in week $t$ than it would have been in the absence of syphilis screening, the ratio $\psi_{t+1}$ would be 95%.

#### 3.3.1.1 Approximating the percent reduction in prevalence of P&S syphilis as a function of the reduction in prevalence of total syphilis

The term $1 - \psi_{t+1}$ is the approximate reduction in prevalence of syphilis of all stages in week $t$. Because screening would be expected to cause a larger relative reduction in total syphilis cases than in P&S syphilis cases, and because syphilis transmission is relatively unlikely beyond the P&S stage, the adjustment term ($\Omega_{STD}$) we applied to account for changes in the prevalence of syphilis in the MSM population over time was a modified version of the ratio $\psi$. Specifically, we calculated the adjustment term $\Omega_{STD}$ in year $t+1$ as $\Omega_{STD} = 1 - \upsilon(1 - \psi_t)$, where $\upsilon$ was set to 0.17 in the base case. That is, the reduction in prevalence of P&S syphilis was assumed to be 0.17 that of the reduction in overall syphilis.

The base case value of 0.17 for $\upsilon$ was calculated based on the average duration (across MSM with and without HIV) of syphilis with and without screening. Based on assumptions described below, the duration of P&S syphilis can be approximated as 15.7 weeks without screening and 14.9 weeks with screening, reflecting a 5% reduction. Also as described below, the average duration of syphilis (all stages) can be approximated as 123 weeks in the absence of screening and 85.8 weeks with screening, a reduction of about 30%. The reduction in P&S duration divided by the reduction in overall duration yields the base case value of $\upsilon$ of 0.17. We calculated $\upsilon$ in this manner because prevalence can be approximated as incidence multiplied by duration. Thus the percentage decline in P&S syphilis...
prevalence (relative to the percentage decline in prevalence of all stages of syphilis) can be approximated by the percentage change in duration of P&S syphilis (relative to the percentage change in duration of all-stages of syphilis). The value of $\nu$ changed when assumptions regarding the frequency of screening were modified.

3.3.2 HIV transmission dynamics

Analogous to the adjustment factor $\Omega_{STD}$, the adjustment term $\Omega_{HIV}$ accounted for changes in the prevalence of HIV in the population over time. This adjustment factor ($\Omega_{HIV}$) in week $t+1$ was calculated as $(HIV_{Prev\_Screen_t}/HIV_{Prev\_NoScreen_t})$, where $HIV_{Prev\_Screen_t}$ is HIV prevalence at week $t$ in the scenario of syphilis screening and $HIV_{Prev\_NoScreen_t}$ is HIV prevalence at week $t$ in the scenario of no syphilis screening.

3.4 Syphilis cofactor effects on the rate of HIV acquisition and transmission

3.4.1 Enhanced susceptibility to HIV

We assumed that syphilis would enhance HIV acquisition. In our model, the rate of HIV incidence among susceptible MSM with syphilis was $\theta$ times that of susceptible MSM without syphilis. We assumed a cofactor effect for acquisition of HIV for MSM with P&S syphilis (vs. those without syphilis) of 3.4 (range: 1.7 to 7), based on the hazard ratio of HIV acquisition of 3.4 among those with incident syphilis in the past 90 days (vs. those without syphilis) reported in a pre-exposure prophylaxis trial of 2,499 MSM and transgender women, which controlled for factors such as condom use, number of partners, STI history, HIV status of sex partner(s) at time of screening, circumcision status, and HSV-2 acquisition. Because our model did not explicitly account for transition from one stage of syphilis to another, we adjusted this hazard ratio for HIV acquisition among those with P&S syphilis to account for the average time spent in the P&S stage. As described below, we assumed that the average time spent in the P&S stage was 13% of the average duration of infection. Accordingly, we adjusted the hazard ratio so that only 13% of the excess risk was applied. Specifically, we calculated the value of $\theta$ as $1 + (0.13 \times 2.4)$, or $\theta = 1.3$ (range: 1.1 to 1.8).

3.4.2 Enhanced HIV infectivity

We assumed that syphilis would enhance HIV transmission. The adjustment factor $\Phi_{HIV}$ accounted for the facilitative effects of syphilis on HIV transmission, under the assumption that the risk
of HIV transmission from a person with HIV and syphilis would be \( \delta \) times that of a person with HIV but without syphilis. Compared to a scenario of no syphilis/HIV co-infection among MSM, the presence of syphilis among MSM with HIV would increase the HIV incidence rate among MSM without HIV in our model by a factor of \((\delta C + (1-C))\), where \(C\) is the percent of MSM with HIV who also have syphilis. The adjustment factor \(\Phi_{\text{HIV}}\) in year \(t+1\) was calculated as: \((\delta C_t + (1-C_t)) / (\delta C_0 + (1-C_0))\), such that the \(\Phi_{\text{HIV}}\) was standardized to a value of 1 in week 0 and would equal 1 in the scenario of no facilitative effects of syphilis on HIV transmission (i.e., \(\Phi_{\text{HIV}} = 1\) when \(\delta = 1\)).

In the base case, we assumed that syphilis in the partner with HIV would increase the probability of syphilis transmission by a factor of 2.5 (range 1.5 to 5), based on a recent model of syphilis and HIV in MSM.\(^{10}\) As with the syphilis cofactor on the risk of HIV acquisition, we adjusted the cofactor for the risk of HIV transmission to account for the average time spent in the P&S stage. As described below, we assumed that the average time spent in the P&S stage was 13% of the average duration of infection. Accordingly, we adjusted the cofactor effect so that only 13% of the excess risk was applied. Specifically, we calculated the value of \(\delta\) as \(1 + (0.13 \times 1.5)\), which yielded \(\delta = 1.2\) (range: 1.1 to 1.5).

### 3.5 Syphilis screening uptake

In the base case, we assumed annual probabilities of screening of 27% for MSM with HIV and 14% for MSM without HIV. The 27% assumption for MSM with HIV was based on annual screening probabilities of about 73% for MSM receiving HIV care,\(^{11}\) multiplied by the estimated percent of MSM with HIV who are HIV diagnosed and retained in care (37%).\(^{12}\) The 14% assumption for MSM without HIV was calculated by multiplying the 27% probability of screening for MSM with HIV by 0.53, where 0.53 is the ratio of syphilis screening uptake in MSM without HIV to that of MSM with HIV based on a survey of MSM in San Francisco.\(^{13}\) In this survey, 34% of MSM without HIV and 64% of MSM with HIV reported being tested for syphilis over the prior 180 days.\(^{13}\) We applied these 34% and 64% values as the upper bound probabilities of screening per year. We applied these as the annual probability of screening rather than the probability of screening per 180 days, so that the estimate for screening uptake for MSM with HIV would be more consistent with national data regarding syphilis testing among MSM in care for HIV.\(^{11}\) For the lower bound values of the annual probability of being tested for syphilis, we reduced the base case values by 50%.
3.6 Duration of syphilis infection in the absence of syphilis screening

Of the estimated 32,215 incident cases in men in 2008 that were eventually diagnosed, 11,255 (34.9%) were diagnosed in the P&S stage, 9,522 (29.6%) were diagnosed in the early latent stage, and 11,438 (35.5%) were diagnosed more than 1 year after infection.²

3.6.1 Duration of cases diagnosed in P&S stage

We assumed an average duration of infection of 4 weeks for those diagnosed in the P&S stage. This 4 week average was approximated assuming an average duration of 20 days and 30 days for those treated in the primary stage and secondary stage, respectively, based on the estimated probability of treatment of 0.05 per day for primary syphilis and 0.1 per day for secondary syphilis.⁸

3.6.2 Duration of cases diagnosed in early latent stage

For those diagnosed in the early latent stage, we assumed 22 weeks in the P&S stage and 15 weeks in the early latent stage. The 22 weeks in the P&S stage was based on the average duration of P&S syphilis in the absence of treatment.⁸ The 15 weeks in the early latent stage reflects the midpoint of the 30-week period between week 22 (the duration of P&S syphilis in the absence of treatment) and week 52 (the cutoff for the early latent stage).

3.6.3 Duration of cases diagnosed more than 1 year after infection

For those diagnosed more than one year after infection, we assumed 22 weeks in the P&S stage, 30 weeks in the early latent stage, and 260 weeks (5 years) in the late and latent stage. The 5 years in the late latent stage was based on the estimated 0.2 annual treatment rate for those in the latent stage.⁸ Under these assumptions, the average duration of infection was estimated at 123 weeks. Lower and upper bound values for the average duration of infection were calculated as 50% and 150% of the base case value.

3.6.4 Average time spent in P&S stage

Based on the assumptions described above, we estimated that the average time spent in the P&S stage as a percent of the average duration of infection was 13%. This value of 13% was calculated as 15.7/123, where 15.7 is the average number of weeks in the P&S stage and 123 is the average duration
of infection in weeks. The value of 15.7 weeks was calculated as a weighted average of the duration of infection for those diagnosed in the P&S stage, the early latent stage, and one year or more after infection (weighted by 34.9%, 29.6%, and 35.5%, respectively, based on the distribution of diagnosed cases described above).

3.7 The rate of recovery from syphilis (r and r̃)

The rate of recovery from syphilis (denoted by r for those without HIV and by r̃ among those with HIV) was a function of three factors: duration of infection in the absence of screening, screening rates, and test sensitivity. Specifically, we set the weekly recovery rate equal to \((1/d) + \sigma \text{SEN}\), where \(d\) is duration of infection (in weeks) in the absence of screening, \(\sigma\) is the weekly screening rate in those without HIV (\(\sigma^\text{HIV}\) for those with HIV), and SEN is test sensitivity. The screening rate was 0 in the scenario of no syphilis screening. As noted above, in the scenario of screening, we assumed annual probabilities of screening of 27% for MSM with HIV and 14% for MSM without HIV. We assumed that syphilis cases detected through screening would be treated successfully, immediately upon detection. Treatment costs were also incurred by those without syphilis who tested positive for syphilis. This treatment is not shown in the model equations above because treatment of false positives did not affect transition from one health state to another.

The values we applied for the syphilis screening test characteristics were as follows: sensitivity (90%, range 80% to 100%) and specificity (90%, range: 80% to 100%). These values reflect the approximate average and range of the estimated sensitivity and specificity of two screening algorithms (initial screen with a nontreponemal test and initial screen with a treponemal test).\(^{14}\)

3.8 Initial distribution across the health states

Our assumption of annual syphilis incidence of 3,290 per 100,000 and a 123 week average duration yielded syphilis prevalence rates of about 7.2% among MSM with HIV. As described above, syphilis prevalence among MSM without HIV was 1.9%. We assumed 20% HIV prevalence among MSM in urban areas.\(^{4}\) Under these assumptions, the initial distribution across the four health states for a population of MSM of 50,000 was as follows:

MSM without syphilis, without HIV (S) = 39,239;
MSM without syphilis, with HIV (Ș) = 9,278;

MSM with syphilis, without HIV (I) = 761;

MSM with syphilis, with HIV (Î) = 722.

4 Health economic assumptions

All cost estimates were updated to 2014 US dollars using the health care component of the Personal Consumption Expenditures price index (http://www.bea.gov/iTable/iTable.cfm?ReqID=12&step=1&acrdn=2).

4.1 Discounted direct medical lifetime cost per case of HIV

We applied $345,000 as the base case value of the discounted, lifetime cost per case of HIV.\textsuperscript{15} We used $264,000 as the lower bound value and $420,000 as the upper bound value, based on the range reported by Farnham et al.’s (2013) when varying the CD4 count at diagnosis.\textsuperscript{15}

4.2 Syphilis screening cost

Syphilis screening costs were calculated as the cost of the screening visit plus the cost of the test. The cost of a screening visit was estimated at $26.50 (range: $10 to $43).\textsuperscript{1,16} We applied a test cost of $7 in 2014 dollars.\textsuperscript{14} The total cost per MSM screened in the base case was thus $33.50 with a range of $17 to $50.

4.3 Syphilis treatment costs and the discounted lifetime direct medical cost per case of syphilis

We applied $98 as the base case cost for syphilis treatment (range: $49 - $154), based on the costs estimated by Owusu-Edusei et al. (2011) for early syphilis ($56; range: $28 to $112) and for late latent syphilis ($112; range: $56 to $168).\textsuperscript{14} The base case value we applied reflects a weighted average of the estimates for early syphilis and late latent syphilis, assuming the latter cost is applicable in 75% of cases based on our description above of the duration of infection. We applied $754 as the estimated discounted lifetime medical cost per case of syphilis,\textsuperscript{17} which includes the possibility of long-term sequelae such as neurosyphilis and cardiovascular syphilis.
In calculating the cost-effectiveness ratios, we assumed the syphilis cases treated as a result of syphilis screening would incur a treatment cost of $98, and all other syphilis cases would incur an average discounted lifetime cost of $754.

4.4 Quality of life assumptions

We assumed that the average, discounted lifetime number of quality-adjusted life years (QALYs) lost for each new HIV infection was 5.8 (range: 4.4 to 8.0). In calculating the number of QALYs gained by syphilis screening, we considered only the QALYs gained by preventing syphilis-attributable HIV infections. We did not include any effects of syphilis on quality of life.

4.5 Cost-effectiveness ratios

We calculated the cost-effectiveness ratios in terms of the cost per QALY gained by syphilis screening (compared to no syphilis screening). The numerator of the cost-effectiveness ratio was calculated as the cost of the syphilis screening program (screening costs plus the costs of syphilis treatment among those testing positive, including false positives), minus the HIV costs and syphilis costs averted by the screening program. The HIV costs averted by the screening program were calculated as the number of HIV cases averted by screening multiplied by the discounted lifetime cost per case of HIV. We calculated lifetime syphilis costs as the number of syphilis cases (minus those treated as a result of syphilis screening) multiplied by the discounted lifetime cost per case of syphilis. For example, in the base case results for the dynamic version of the model, there were 5,778 discounted syphilis cases in the screening scenario, of which 2,050 discounted syphilis cases were treated as a result of the screening program, leaving 3,728 cases. In contrast, there were 5,992 discounted syphilis cases in the no screening scenario. We calculated the averted syphilis costs as \((5,992 - 3,728)\times \$754\), where \$754 is the base case value of the expected lifetime cost per case of syphilis. The denominator of the cost-effectiveness ratio was the number of QALYs gained by preventing syphilis-attributable HIV infections.

5 Probabilistic sensitivity analyses

In addition to the one-way and two-way sensitivity analyses described in the main text, we also conducted probabilistic analyses in which the model was run 15,000 times, and in each model run a random value was selected for each parameter listed in Appendix Table 3. Except for sensitivity and specificity (see below), we assumed a lognormal distribution for all of these parameters, based on the
following justification. We used the lognormal distribution for cost parameters because this is a common practice in health economic studies. That is, the lognormal distribution is often used to capture uncertainty in cost parameters, given that the cost estimates cannot be negative and cost estimates are typically right-skewed. Because the other parameters in Appendix Table 3 (except sensitivity and specificity) are also constrained to be non-negative and potentially right-skewed, we used the lognormal distribution for these parameters as well. These parameters were the annual syphilis incidence rate per 100,000 MSM without HIV, annual syphilis incidence rate per 100,000 MSM with HIV, annual HIV incidence rate among those without syphilis, syphilis cofactor effect on HIV acquisition, syphilis cofactor effect on HIV transmission, annual syphilis screening rate among MSM without HIV, annual syphilis screening rate among MSM with HIV, initial HIV prevalence, average duration of syphilis (weeks) in the absence of syphilis screening, and lifetime number of QALYs lost per HIV case.

Our methods for estimating the lognormal distribution parameters followed those of Elbasha and Dasbach (2010). We approximated the standard error (SE) as the range divided by 2*1.96, where the range is the upper bound value minus the lower bound value. The parameter \( \mu \) was calculated as \( \ln(\text{BASE}) - 0.5\ln[1+(\text{SE}^2/\text{BASE}^2)] \), where BASE is the base case value and \( \ln \) indicates the natural log. The parameter \( \sigma \) was calculated as the square root of \( \ln[1+(\text{SE}^2/\text{BASE}^2)] \). For the beta distribution, the standard error (SE) was approximated as described above for the lognormal distribution. The parameter \( \alpha \) was calculated as \( \text{BASE}[(1-\text{BASE})\text{BASE} - \text{SE}^2]/\text{SE}^2 \). The parameter \( \beta \) was calculated as \( [1-\text{BASE}][(1-\text{BASE})\text{BASE} - \text{SE}^2]/\text{SE}^2 \).

To take into account the inverse correlation between sensitivity and specificity, specificity was assumed to follow a beta distribution and sensitivity was calculated as a function of specificity and the diagnostic odds ratio (DOR), which we assumed followed a lognormal distribution. This approach is commonly used in probabilistic sensitivity analyses. We used the following formula for DOR to calculate sensitivity as a function of DOR and specificity:

\[ DOR = \frac{\text{sensitivity} \times \text{specificity}}{(1-\text{sensitivity}) \times (1-\text{specificity})}. \]

In the base case, we assumed sensitivity = 0.9 and specificity = 0.9. These two values correspond to a DOR of 81. We also assumed a lower bound value of 0.8 for both sensitivity and specificity. Simultaneously setting both of these values to their lower bound of 0.8 yields a DOR of 16. To account for the DOR of 81 under base case assumptions and the DOR of 16 in the worst case...
scenario of test performance, we applied a lognormal distribution for the DOR with parameters (4.4, 0.5). The 4.4 parameter was chosen so that the median value of the DOR in the sensitivity analyses would be 81, and the 0.5 parameter was chosen such that the DOR would exceed 16 in virtually every simulation. Our assumptions about the median and range of the DOR are quite conservative compared to the median DOR of 737 and interquartile range of 210 – 1,443 reported by Tucker and colleagues (2010) in their systematic review of rapid syphilis testing in low-income settings. Had we instead applied a distribution for the DOR consistent with the estimates of Tucker and colleagues, the resulting distribution of cost-effectiveness estimates in the probabilistic sensitivity analyses would have been much more favorable towards screening.

In addition to accounting for the inverse correlation between sensitivity and specificity, we also assumed that certain other pairs or trios of parameters were correlated. Specifically, we assumed that: initial HIV prevalence was positively correlated with the annual HIV incidence rate at the onset of the screening program; the syphilis incidence rate among those with HIV was positively correlated with the syphilis incidence rate among those without HIV; the rate of syphilis screening among those with HIV was positively correlated with the rate of syphilis screening among those without HIV; the cost of syphilis testing and the cost of syphilis treatment were correlated with each other and the lifetime cost per case of syphilis; and the syphilis cofactor effect on HIV acquisition was positively correlated with the syphilis cofactor effect on HIV transmission. In doing so, we assumed a perfect correlation within each pair of parameters (e.g., in each simulation the p-value for the random value for initial HIV prevalence was the same as the p-value for the random value of the annual HIV incidence rate, the p-value for the random value of the syphilis incidence rate among those with HIV was the same as the p-value for the random value of the annual syphilis incidence rate among those without HIV, and so on). These assumptions about correlations between parameters other than sensitivity and specificity did not have a substantial effect on the results of the probabilistic sensitivity analyses, particularly for the dynamic model.

6 Appendix references


# Appendix tables

## Appendix Table 1: Summary of symbols used in model equations

<table>
<thead>
<tr>
<th>Model component</th>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MSM without syphilis, without HIV</td>
<td>$S_t$</td>
<td>These are the four health states in the model. The subscript $t$ denotes week. The initial values for $S$, $S_t$, $I$ and $I_t$ are assumed as described in appendix text, and the subsequent values are determined according to the model equations.</td>
</tr>
<tr>
<td>Number of MSM without syphilis, with HIV</td>
<td>$S^\ast_t$</td>
<td></td>
</tr>
<tr>
<td>Number of MSM with syphilis, without HIV</td>
<td>$I_t$</td>
<td></td>
</tr>
<tr>
<td>Number of MSM with syphilis, with HIV</td>
<td>$I^\ast_t$</td>
<td></td>
</tr>
<tr>
<td>Incidence of syphilis among those without HIV</td>
<td>$\lambda_{STD}$</td>
<td>$\lambda_{STD}$ and $\hat{\lambda}_{STD}$ represent the incidence rate of syphilis at the onset of the screening program among those without and with HIV, respectively.</td>
</tr>
<tr>
<td>Incidence of syphilis among those with HIV</td>
<td>$\hat{\lambda}_{STD}$</td>
<td></td>
</tr>
<tr>
<td>Incidence of HIV among those without syphilis</td>
<td>$\lambda_{HIV}$</td>
<td>$\lambda_{HIV}$ represents the incidence rate of HIV at the onset of the screening program among those without syphilis.</td>
</tr>
<tr>
<td>Syphilis cofactor effect on HIV acquisition (Relative rate of HIV incidence among those with syphilis vs. those without syphilis)</td>
<td>$\theta$</td>
<td>The HIV incidence rate among those with syphilis was $\theta$ times that of those without syphilis, due to facilitative effects of syphilis.</td>
</tr>
<tr>
<td>Adjustment factor to account for dynamic changes in HIV prevalence over time</td>
<td>$\Omega_{HIV}$</td>
<td>Example: If HIV prevalence in the scenario of syphilis screening is 5% lower in week $t$ than it would have been in the absence of syphilis screening, the probability of acquiring HIV (among those susceptible) in week $t$ is adjusted to be 5% lower than it would have been in the absence of screening.</td>
</tr>
<tr>
<td>Adjustment factor to account for dynamic changes in syphilis prevalence over time</td>
<td>$\Omega_{STD}$</td>
<td>Example: If P&amp;S syphilis prevalence in the scenario of syphilis screening is 5% lower in week $t$ than it would have been in the</td>
</tr>
<tr>
<td>Model component</td>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>--------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>absence of syphilis screening, the probability of acquiring syphilis (among those susceptible) in week $t$ is adjusted to be 5% lower than it would have been in the absence of screening. Given that our model did not specifically account for stage of syphilis, we assumed that the reduction in P&amp;S syphilis prevalence as a result of screening would be 17% of the overall reduction in syphilis, as described elsewhere in this appendix.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjustment factor to account for the facilitative effects of syphilis on HIV transmission</td>
<td>$\Phi_{\text{HIV}}$</td>
<td>The adjustment factor was calculated as described in the appendix text under the assumption that the risk of HIV transmission from a person with HIV and syphilis is $\delta$ times that of a person with HIV but without syphilis. See the appendix text and Appendix Table 2 for a description of $\delta$ and $\Phi_{\text{HIV}}$.</td>
</tr>
<tr>
<td>Recovery rate from syphilis for those without HIV</td>
<td>$r$</td>
<td>The clearance rate was calculated as $(1/d) + \sigma \text{SEN}$, where $d$ is duration of infection (in weeks) in the absence of screening, $\sigma$ is the weekly screening rate in those without HIV ($\hat{\sigma}$ for those with HIV), and SEN is test sensitivity. See the appendix text and Appendix Table 2 for a description of $d$, $\sigma$, $\hat{\sigma}$, and $S$.</td>
</tr>
</tbody>
</table>
### Appendix Table 2: Summary of model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Base case assumption</th>
<th>Value applied in model: Base case (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis incidence rate among those without HIV$^{3,9}$</td>
<td>$\lambda_{STD}$</td>
<td>Annual rate: 820 per 100,000</td>
<td>Weekly rate per 100,000: 15.8 (8.8 to 21.9)</td>
</tr>
<tr>
<td>Syphilis incidence rate among those with HIV$^{3,9}$</td>
<td>$\lambda_{STD}$</td>
<td>Annual rate: 3,290 per 100,000</td>
<td>Weekly rate per 100,000: 63.3 (35.2 to 87.7)</td>
</tr>
<tr>
<td>Syphilis screening rate, MSM without HIV$^{11,13}$</td>
<td>$\sigma$</td>
<td>14% annual probability of being screened</td>
<td>Weekly rate: 0.0029 (0.0013 to 0.0081)</td>
</tr>
<tr>
<td>Syphilis screening rate, MSM with HIV$^{11,13}$</td>
<td>$\hat{\sigma}$</td>
<td>27% annual probability of being screened</td>
<td>Weekly rate: 0.0061 (0.0029 to 0.0196)</td>
</tr>
<tr>
<td>Average duration of syphilis in absence of screening</td>
<td>$d$</td>
<td>123 weeks</td>
<td>See r and $\bar{r}$ below</td>
</tr>
<tr>
<td>Syphilis co-factor on rate of HIV acquisition$^{9}$</td>
<td>$\theta$</td>
<td>We assumed a cofactor effect of 3.4 for P&amp;S syphilis on HIV acquisition, based on the hazard ratio of HIV acquisition among those with incident syphilis in the past 90 days vs. those without incident syphilis. This 3.4 cofactor effect was multiplied by 13%, where 13% is the average time spent</td>
<td>1.3 (1.1 to 1.8)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Symbol</td>
<td>Base case assumption</td>
<td>Value applied in model: Base case (range)</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>in the P&amp;S stage as a percent of the average duration of infection. This adjustment was calculated as: 1 + 0.13*(3.4-1) = 1.3.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis co-factor on rate of HIV transmission$^{10}$</td>
<td>δ</td>
<td>HIV transmission from index patient with P&amp;S syphilis was assumed to be 2.5 times as likely as HIV transmission from index patient without syphilis. This 2.5 cofactor effect was adjusted as described in the preceding row. This adjustment was calculated as: 1 + 0.13*(2.5-1) = 1.2.</td>
<td>1.2 (1.1 to 1.5)</td>
</tr>
<tr>
<td>Incidence of HIV among those without syphilis$^{6}$</td>
<td>$\lambda_{HIV}$</td>
<td>Annual incidence rate: 1.6% Based on average of two estimates of overall HIV incidence among MSM: 2.25% from a literature review$^{6}$ and 0.9% based on the estimated 29,800 new cases of HIV in men acquired from male-to-male sexual contact in 2010$^{7}$ combined with the MSM</td>
<td>Weekly rate per 100,000: 30.8 (15.4 to 46.2)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Symbol</td>
<td>Base case assumption</td>
<td>Value applied in model: Base case (range)</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Rate of recovery from syphilis, MSM without HIV</td>
<td>r</td>
<td>0.00813 weekly rate in absence of screening, calculated as 1/d, where d = 123 as noted above. With screening, r was calculated as 0.00813 plus the product of the weekly screening rate and test sensitivity.</td>
<td>Weekly rate: 0.0107 (0.0093 – 0.0154)</td>
</tr>
<tr>
<td>Rate of recovery from syphilis, MSM with HIV</td>
<td>ř̅</td>
<td>0.00813 weekly rate in absence of screening, calculated as 1/d, where d = 123 as noted above. With screening, ř̅ was calculated as 0.00813 plus the product of the weekly screening rate and test sensitivity.</td>
<td>Weekly rate: 0.0136 (0.0107 – 0.0258)</td>
</tr>
<tr>
<td>Syphilis test sensitivity$^{14}$</td>
<td>SEN</td>
<td>0.90</td>
<td>0.90 (0.8 to 1)</td>
</tr>
<tr>
<td>Syphilis test specificity$^{14}$</td>
<td></td>
<td>0.90</td>
<td>0.90 (0.8 to 1)</td>
</tr>
</tbody>
</table>

Rates not indicated as “per 100,000” are per person. No symbol is provided for syphilis test specificity because specificity is not included in the model equations, as treatment of false positives does not cause a transition from one health state to another. However, specificity affects the costs of screening, as costs are incurred by providing syphilis treatment to those without syphilis who test positive, and these costs are included in the calculation of the cost-effectiveness ratios.
### Appendix Table 3. Distributions used in probabilistic sensitivity analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case value (range)</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual syphilis incidence rate per 100,000 MSM without HIV ((\lambda_{STD}))</td>
<td>820 (460 - 1140)</td>
<td>lognormal (6.69,0.21)</td>
</tr>
<tr>
<td>Annual syphilis incidence rate per 100,000 MSM with HIV ((\lambda^*_{STD}))</td>
<td>3290 (1830 - 4560)</td>
<td>lognormal (8.08,0.21)</td>
</tr>
<tr>
<td>Annual HIV incidence rate among those without syphilis ((\lambda_{HIV}))</td>
<td>0.016 (0.008 - 0.024)</td>
<td>lognormal (-4.17,0.25)</td>
</tr>
<tr>
<td>Syphilis cofactor effect on HIV acquisition ((\theta))</td>
<td>1.3 (1.1 - 1.8)</td>
<td>lognormal (-1.36,0.55)</td>
</tr>
<tr>
<td>Syphilis cofactor effect on HIV transmission ((\delta))</td>
<td>1.2 (1.1 - 1.5)</td>
<td>lognormal (-1.73,0.48)</td>
</tr>
<tr>
<td>Annual syphilis screening rate, MSM without HIV</td>
<td>0.151 (0.07 - 0.42)</td>
<td>lognormal (-2.04,0.55)</td>
</tr>
<tr>
<td>Annual syphilis screening rate, MSM with HIV</td>
<td>0.315 (0.15 - 1.02)</td>
<td>lognormal (-1.36,0.63)</td>
</tr>
<tr>
<td>Syphilis test sensitivity</td>
<td>0.9 (0.8 - 1)</td>
<td>Not applicable**</td>
</tr>
<tr>
<td>Syphilis test specificity</td>
<td>0.9 (0.8 - 1)</td>
<td>beta (30.22,3.36)</td>
</tr>
<tr>
<td>Initial HIV prevalence</td>
<td>0.2 (0.1 - 0.3)</td>
<td>lognormal (-1.64,0.25)</td>
</tr>
<tr>
<td>Average duration of syphilis (weeks) in absence of syphilis screening</td>
<td>123 (61.5 - 184.5)</td>
<td>lognormal (4.78,0.25)</td>
</tr>
<tr>
<td>Lifetime number of QALYs lost per HIV case</td>
<td>5.8 (4.4 - 8)</td>
<td>lognormal (1.75,0.16)</td>
</tr>
<tr>
<td>Lifetime cost per case of HIV</td>
<td>345,000 (264,000 – 420,000)</td>
<td>lognormal (12.74,0.11)</td>
</tr>
<tr>
<td>Lifetime cost per case of syphilis</td>
<td>754 (377 - 1131)</td>
<td>lognormal (6.59,0.25)</td>
</tr>
<tr>
<td>Cost of syphilis screening</td>
<td>33.5 (17 - 50)</td>
<td>lognormal (3.48,0.25)</td>
</tr>
</tbody>
</table>
Cost of syphilis treatment  
98 (49 - 154)  
lognormal (4.55,0.27)

Diagnostic odds ratio  
Not applicable**  
lognormal (4.4,0.5)

Assumptions and sources for the base case values and ranges are described in detail in Sections 3 and 4 of this appendix and are summarized in Table 1 of the main manuscript. All costs are in 2014 US dollars.

*In the probabilistic sensitivity analysis, the cofactor effects were calculated assuming a lognormal distribution of the excess risk attributable to syphilis. Specifically the syphilis cofactor effect on HIV acquisition ($\theta$) was calculated as $1 + x$, where $x$ was assumed to follow the lognormal distribution (-1.36,0.55) and the syphilis cofactor effect on HIV transmission ($\delta$) was calculated as $1 + y$, where $y$ was assumed to follow the lognormal distribution (-1.73,0.48).

**Values for the syphilis test sensitivity in the probabilistic sensitivity analyses were calculated based on the value obtained for specificity and the value obtained for the diagnostic odds ratio as described in Section 5 of this appendix. The diagnostic odds ratio was used only in the probabilistic sensitivity analyses; it was not used in the main analyses and one-way sensitivity analyses.