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The Cost-Effectiveness of Syphilis Screening Among Men Who Have Sex With Men: An Exploratory Modeling Analysis

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Abstract

We adapted a published model to estimate the costs and benefits of screening men who have sex with men for syphilis, including the benefits of preventing syphilis-attributable human immunodeficiency virus. The cost per quality-adjusted life year gained by screening was <US \$0 (cost-saving) and US \$16,100 in the dynamic and static versions of the model, respectively.

Approximately three fourths of reported primary and secondary (P&S) syphilis cases in the United States occur among men who have sex with men (MSM).¹ Because of the disproportionate burden of syphilis among MSM, and because syphilis can facilitate human immunodeficiency virus (HIV) acquisition and transmission,^{2–4} the Centers for Disease Control and Prevention recommends that sexually active MSM be tested for syphilis at least annually.⁵ More frequent screening (ie, every 3 to 6 months) is recommended for MSM with risk factors for syphilis, such as having multiple sex partners.⁵ The purpose of this study was to estimate the cost-effectiveness of syphilis screening among MSM in the United States.

We adapted a previously published model of the impact and cost-effectiveness of screening MSM for rectal chlamydial and gonococcal infection.⁶ The previous model accounted for increased susceptibility to HIV among MSM with rectal sexually transmitted infections. We adapted the model to include both increased susceptibility to HIV among HIV-negative MSM with syphilis and increased infectiousness of HIV among HIV-positive MSM with syphilis (Fig. 1).

Our model is exploratory in nature and includes 3 main simplifying features. First, we did not stratify the MSM population by level of sexual activity, age, or any other factor besides syphilis status and HIV status. Second, we did not explicitly model the mixing of sex partners; instead, the model applied weekly syphilis and HIV incidence rates based on the literature, and these rates were adjusted each week to account for changes in syphilis prevalence and HIV prevalence in the population. Third, we did not explicitly model the different stages of syphilis. Instead, we assumed that any cofactor effect of syphilis on HIV transmission would occur in the primary and secondary stages, and the value we applied for

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the cofactor effect was adjusted according to our assumption regarding the time spent in the P&S stage as a percent of the average duration of infection. We made this simplifying and conservative assumption because of the lack of stage-specific data on the cofactor effect of syphilis on HIV transmission. Parameter values and sources are listed in Table 1. All costs were updated to 2014 US dollars. A technical appendix, (<http://links.lww.com/OLQ/A132>) provides a detailed description of the model.

We used 2 versions of the model: a static version and a dynamic version. The static version accounted only for syphilis cofactor effects on the probability of HIV acquisition and did not account for dynamic changes in syphilis prevalence and HIV prevalence in the population. The dynamic version accounted for population-level reductions in syphilis prevalence and HIV prevalence over time as a result of syphilis screening, and included syphilis cofactor effects on the probability of HIV acquisition (for HIV-negative MSM with syphilis) and the probability of HIV transmission (for HIV-positive MSM with syphilis).

The study question we addressed is: what is the cost-effectiveness of syphilis screening among MSM aged 15 to 64 years in the United States, compared with a strategy of no syphilis screening? In the base case, we assumed annual screening rates of 0.31 for MSM with HIV and 0.15 for MSM without HIV.^{9,10} We used a societal perspective and included syphilis screening costs, syphilis treatment costs, and HIV treatment costs; however, we did not include nonmedical costs, such as patient time and transportation costs or productivity costs. The only health benefits that we included were the quality-adjusted life years (QALYs) gained by preventing HIV; we did not include QALYs gained by treating syphilis in and of itself. We used a 10-year time frame to assess syphilis screening costs and the number of HIV cases and syphilis cases averted by syphilis screening. We used a lifetime analytic horizon to assess the treatment costs averted by preventing HIV and syphilis as well as the QALYs gained by preventing HIV.

We conducted 1-way sensitivity analyses in which we calculated the cost per QALY gained by syphilis screening when varying each of the parameters in Table 1, 1 parameter at a time from its lower bound to its upper bound value, while holding the other parameters at their base case values. We conducted a 2-way sensitivity analyses in which we simultaneously varied the syphilis burden (the syphilis incidence rate among those with and without HIV) and the HIV burden (the HIV incidence rate and initial HIV prevalence). We also conducted multiway sensitivity analyses to examine how the results changed when all the parameters listed in Table 1 were varied simultaneously. Specifically, we conducted probabilistic sensitivity analyses in which the model was run 15,000 times, and in each model run, a random value was selected for each parameter (see technical appendix for details, <http://links.lww.com/OLQ/A132>). Briefly, we assumed a lognormal distribution for each parameter, except for sensitivity and specificity. To account for the inverse correlation between sensitivity and specificity, we calculated sensitivity based on specificity (for which we assumed a β distribution) and the diagnostic odds ratio (for which we assumed a lognormal distribution).^{8,13}

In the base case, syphilis screening resulted in a decline in syphilis prevalence of over 30% over the 10-year time frame (Table 2). The cost per QALY gained was US \$16,100 in the

static version of the model and <US \$0 (cost-saving) in the dynamic version of the model (Table 2). In the 1-way sensitivity analyses, the estimated cost per QALY gained by syphilis screening ranged from <US \$0 to \$233,000 in the static version of the model and remained <US \$0 in all scenarios in the dynamic version of the model (Table 3). The 4 most influential parameters were the duration of syphilis in the absence of screening, the syphilis cofactor on HIV acquisition, the incidence of syphilis among MSM without HIV, and the incidence of HIV. When we simultaneously varied the burden of syphilis and the burden of HIV, the cost per QALY gained by screening ranged from <US \$0 to \$196,800 in the static version of the model and remained <US \$0 in the dynamic version of the model (Table 3). In the probabilistic sensitivity analyses, the range of estimates for the cost per QALY gained by syphilis screening (based on the 2.5th and 97.5th percentiles of simulations) was <US \$0 to \$362,100 in the static version of the model and <US \$0 to \$10,700 in the dynamic version of the model (Table 3).

Our exploratory modeling exercise suggested that screening MSM for syphilis can be a cost-effective HIV prevention tool, particularly when considering the potential dynamic effects of screening. The base-case results from our dynamic version of the model suggested that the syphilis screening of MSM could pay for itself by averting the treatment costs of syphilis sequelae and syphilis-attributable HIV. The health benefits we included in our analysis were limited to the QALYs gained by preventing HIV, and our estimates of the cost effectiveness of syphilis screening would have been more favorable had we included the QALYs gained by averted syphilis sequelae. In fact, Tuite and colleagues¹⁴ found that enhanced syphilis screening of HIV-positive MSM in Canada could be cost-effective when considering the benefits of reduced syphilis sequelae, without consideration of synergistic effects of syphilis on HIV transmission.

One of the most important limitations of our study is the uncertainty in the parameter values we applied in the model. For example, our results were highly sensitive to assumptions regarding the syphilis cofactor effect on HIV acquisition. Although the potential for syphilis to facilitate the spread of HIV has been documented extensively,^{2–4} it is difficult to determine the precise magnitude of this impact. However, in 1-way sensitivity analyses using our dynamic model, syphilis screening was cost-saving even when applying the lower-bound value of 1.1 for the syphilis cofactor effect on HIV acquisition. We also note that our assessment of the benefits of syphilis screening among MSM might be conservative because we included only the health benefits accrued in MSM. We did not include the possibility that screening MSM for syphilis could reduce the burden of syphilis in other populations, such as women.

Another important limitation is our use of a simplified, exploratory model which does not explicitly account for (1) transition from one stage of syphilis to another, (2) age and sexual activity level, and (3) mixing of sex partners. The effect of these assumptions is unclear and illustrates the need to develop more complex models to assess more rigorously the costs and benefits of syphilis screening. One such model, an agent-based transmission model developed by Hoare and colleagues,⁴ showed that syphilis screening among MSM could substantially reduce syphilis and HIV incidence among MSM in Australia. Their model

suggested possible reductions of almost 50% in HIV incidence among MSM within 10 years as a result of Australia's syphilis action plan.

Despite limitations and incomplete data, our model offers a useful approximation of the potential health impact and cost-effectiveness of syphilis screening among MSM in the United States. We found that syphilis screening among MSM can be a cost-saving tool to prevent HIV, as long as syphilis does indeed facilitate HIV acquisition and transmission to the degree we assumed. Our findings highlight the need for data on the cofactor effect of syphilis on HIV acquisition and transmission, particularly in regard to how the cofactor effect varies by stage of syphilis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Model schematic. The 4 health states are mutually exclusive, and transition occurs when syphilis is acquired, when syphilis is treated, or when HIV is acquired. The HIV incidence rate among those without syphilis is $\lambda_{\text{HIV}}\Omega_{\text{HIV}}\Phi_{\text{HIV}}$, where λ_{HIV} is the HIV incidence rate among MSM without syphilis at the onset of the screening program, Ω_{HIV} is an adjustment factor to account for changes in the prevalence of HIV in sex partners over time, and Φ_{HIV} is an adjustment factor to account for changes in syphilis and HIV coinfection in sex partners over time. The adjustment term Φ_{HIV} is calculated based on syphilis/HIV coinfection rates and the syphilis cofactor effect on HIV transmission δ (acquiring HIV from a partner with HIV and syphilis is assumed to be δ times as likely as acquiring HIV from a partner with HIV who is not coinfecting with syphilis). The syphilis cofactor effect on HIV acquisition is θ (ie, the rate of HIV incidence among those with syphilis is assumed to be θ times that of those without syphilis). The incidence rate of syphilis is $\lambda_{\text{STD}}\Omega_{\text{STD}}$ and $\hat{\lambda}_{\text{STD}}\Omega_{\text{STD}}$ among those without and with HIV, respectively, where λ_{STD} and $\hat{\lambda}_{\text{STD}}$ are the incidence rates of syphilis at the onset of the screening program among those without and with HIV, respectively, and Ω_{STD} is an adjustment factor to account for changes in the prevalence of syphilis in sex partners over time as a result of the syphilis screening program. Syphilis clearance rates among those without and with HIV are denoted by r and $\hat{r}$, respectively.

TABLE 1.
Parameter Values Used in Model of Cost-Effectiveness of Screening MSM for Syphilis to Prevent HIV

Parameter	Base Case	Lower Bound	Upper Bound	Source
Annual syphilis incidence rate per 100,000 MSM without HIV (λ_{STD})	820	460	1,140	Calculated [*]
Annual syphilis incidence rate per 100,000 MSM with HIV ($\hat{\lambda}_{STD}$)	3,290	1,830	4,560	Calculated [*]
Annual HIV incidence rate among those without syphilis (λ_{HIV})	1.6%	0.8%	2.4%	7, 11–12 [†]
Syphilis cofactor effect on HIV acquisition (θ)	1.3	1.1	1.8	15 [‡]
Syphilis cofactor effect on HIV transmission (ϕ)	1.2	1.1	1.5	4 [‡]
Annual syphilis screening rate, MSM without HIV	0.151	0.07	0.42	9,10
Annual syphilis screening rate, MSM with HIV	0.315	0.15	1.02	9,10
Syphilis test sensitivity	0.9	0.8	1.0	16
Syphilis test specificity	0.9	0.8	1.0	16
Initial HIV prevalence	0.20	0.10	0.30	17
Average duration of syphilis (weeks) in absence of syphilis screening	123	61.5	184.5	See appendix, http://links.lww.com/OLQ/A132
Lifetime number of QALYs lost per HIV case	5.8	4.4	8.0	18
Lifetime cost per case of HIV	\$345,000	\$264,000	\$420,000	18
Lifetime cost per case of syphilis	\$754	\$377	\$1,131	19
Cost of syphilis screening	\$33.50	\$17	\$50	16,20
Cost of syphilis treatment	\$98	\$49	\$154	16

We applied a weekly rate of recovery from syphilis in the absence of screening of (1/123), were 123 is the estimated average duration of syphilis (in weeks) in the absence of screening based on Gamett et al. (1997)²¹ as described in the appendix. With screening, the weekly rate of recovery was calculated as (1/123) plus the product of the weekly screening rate and test sensitivity.

All costs are in 2014 US dollars, updated for inflation using the health care component of the Personal Consumption Expenditures index (<http://www.bea.gov/Table/Table.cfm?ReqID=12&step=1&acrdn=2>).

See technical appendix for a detailed description of model assumptions and sources, <http://links.lww.com/OLQ/A132>.

^{*} Syphilis incidence rates among MSM aged 15 to 64 years were approximated based on 17,967 reported P&S cases in men in this age group in 2014, of which 83.1% are assumed to be in MSM (Centers for Disease Control and Prevention surveillance data), multiplied by 3.6 to account for underreporting.²² The population size of MSM for the denominator (4.09 million) was calculated assuming 3.9% of men are MSM.¹¹ Rates for MSM with and without HIV were calculated assuming 20% HIV prevalence among MSM¹⁷ and that MSM with HIV account for 50% of MSM syphilis cases.¹

[†] HIV incidence among MSM without syphilis was calculated as the average of two published estimates: 2.25% from a literature review¹² and 0.9% based on the estimated 29,800 new cases of HIV in men acquired from male-to-male sexual contact in 2010⁷ combined with the MSM population and HIV prevalence assumptions noted above.

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[‡]We assumed syphilis cofactor effects of 3.4 for HIV acquisition¹⁵ and 2.5 for HIV transmission.⁴ However, we assumed these cofactor effects would be applicable only during P&S syphilis. Because our model does not explicitly account for stage of syphilis, we adjusted these cofactor effects so that only 13% of the excess risk was applied, where 13% is the estimated average time spent in the P&S stage as a percent of the average duration of syphilis.

TABLE 2.
Estimated Impact, Cost, and Cost Per QALY Gained by Screening MSM for Syphilis^{*}

Model Result	Static Version of Model [†]	Dynamic Version of Model
Prevalence of syphilis in MSM after 10 y [‡]	2.36%	2.22%
Percent reduction in syphilis prevalence due to screening	32.0%	36.1%
Number of HIV cases averted by syphilis screening	5.2	33.0
Costs of screening program (test costs and treatment costs)	US \$3,800,300	US \$3,792,300
HIV treatment costs averted	US \$1,778,900	US \$11,392,700
Syphilis medical costs averted	US \$1,539,800	US \$1,707,400
Incremental cost (compared to no screening)	US \$481,600	−US \$9,307,900
Incremental number of QALYs gained (compared to no screening)	29.9	191.5
Cost effectiveness ratio (incremental cost per QALY compared to no screening)	\$16,100	< \$0 (cost-saving)

Future costs and health outcomes were discounted at 3% annually. The costs of the screening program include treatment costs for those testing positive, including false positives.

^{*} All costs estimates are in 2014 US dollars, rounded to nearest \$100.

[†] Results from static version of model include benefits of screening and treatment only to those who are screened (ie, indirect effects of screening are not included).

[‡] In the absence of screening, syphilis prevalence was 3.47% after 10 years.

The cost-effectiveness ratio shows the incremental cost per QALY gained by syphilis screening of MSM compared to no screening.

Base Case Results and Sensitivity Analyses: Incremental Cost Per QALY Gained by Screening MSM for Syphilis When Varying One or More Parameter Values

TABLE 3.

Parameter Varied	Static Version of Model	Dynamic Version of Model
None (base case parameter values)	16,100	<0
One-way sensitivity analyses		
Incidence of syphilis, MSM without HIV (λ_{STD})	<0 to 85,000	<0
Incidence of syphilis, MSM with HIV ($\hat{\lambda}_{STD}$)	6300 to 28,500	<0
HIV incidence rate among those without syphilis (λ_{HIV})	<0 to 78,300	<0
Syphilis cofactor effect on HIV acquisition (θ)	<0 to 165,200	<0
Syphilis cofactor effect on HIV transmission (δ)	Not applicable	<0
Syphilis screening rate	1800 to 70,800	<0
Syphilis test sensitivity	6800 to 27,800	<0
Syphilis test specificity	<0 to 42,700	<0
Initial HIV prevalence	8100 to 26,500	<0
Average duration of syphilis in the absence of screening	<0 to 233,000	<0
Lifetime number of QALYs lost per HIV case	11,700 to 21,200	<0
Lifetime cost per case of HIV	3200 to 30,100	<0
Cost of syphilis screening	<0 to 62,200	<0
Cost of syphilis treatment	<0 to 35,300	<0
Lifetime cost per case of syphilis	<0 to 41,900	<0
Two-way sensitivity analyses: syphilis burden and HIV burden *		
Low syphilis burden and low HIV burden	196,800	<0
Low syphilis burden and high HIV burden	85,600	<0
High syphilis burden and low HIV burden	16,300	<0
High syphilis burden and high HIV burden	<0	<0
Probabilistic sensitivity analysis		
5th and 95th percentiles of 15,000 simulations	<0 to 261,600	<0
2.5th and 97.5th percentiles of 15,000 simulations	<0 to 362,100	<0 to 10,700

Cost per QALY estimates are reported in 2014 US dollars and rounded to the nearest US \$100. For 4 parameters (the cost of syphilis screening, the cost of syphilis treatment, the syphilis screening rate, and the initial HIV prevalence), applying the lower bound value in the 1-way sensitivity analyses resulted in a lower cost per QALY than applying the upper bound value. For all other parameters, applying the lower bound value resulted in a higher cost per QALY than applying the upper bound value.

* When varying the syphilis burden, we varied the syphilis incidence rate among those with and without HIV. Initial syphilis prevalence was calculated based on syphilis incidence and duration assumptions. When varying the HIV burden, we varied the HIV incidence rate and initial HIV prevalence.