Estimation of the Lifetime Quality-Adjusted Life Years (QALYs) Lost Due to Syphilis Acquired in the United States in 2018

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Background. The purpose of this study was to estimate the health impact of syphilis in the United States in terms of the number of quality-adjusted life years (QALYs) lost attributable to infections in 2018.

Methods. We developed a Markov model that simulates the natural history and management of syphilis. The model was parameterized by sex and sexual orientation (women who have sex with men, men who have sex with women [MSW], and men who have sex with men [MSM]), and by age at primary infection. We developed a separate decision tree model to quantify health losses due to congenital syphilis. We estimated the average lifetime number of QALYs lost per infection, and the total expected lifetime number of QALYs lost due to syphilis acquired in 2018.

Results. We estimated the average number of discounted lifetime QALYs lost per infection as 0.09 (95% uncertainty interval [UI] .03–.19). The total expected number of QALYs lost due to syphilis acquired in 2018 was 13 349 (5071–31 360). Although per-case loss was the lowest among MSM (0.06), MSM accounted for 47.7% of the overall burden. For each case of congenital syphilis, we estimated 1.79 (1.43–2.16) and 0.06 (.01–.14) QALYs lost in the child and the mother, respectively. We projected 2332 (1871–28 250) and 79 (17–177) QALYs lost for children and mothers, respectively, due to congenital syphilis in 2018.

Conclusions. Syphilis causes substantial health losses in adults and children. Quantifying these health losses in terms of QALYs can inform cost-effectiveness analyses and can facilitate comparisons of the burden of syphilis to that of other diseases.

Keywords. syphilis; burden of disease; quality-adjusted life years; sexually transmitted disease.

Syphilis, a sexually transmitted genital ulcerative disease caused by infection with *Treponema pallidum*, can cause a range of adverse health outcomes if left untreated, including severe outcomes relating to pregnancy. In the United States in 2019, there were 129 813 diagnosed syphilis cases, the highest number reported since 1991, and 1870 reported cases of congenital syphilis, which was 4-fold higher than diagnoses in 2013 [1]. Considering this large and rising burden, estimates of the lifetime costs and number of quality-adjusted life years (QALYs) lost per infection can quantify the public health and economic impact of syphilis

infections and inform cost-effectiveness analyses of interventions to prevent syphilis. A recent modelling study estimated that the average discounted lifetime cost per infection is $1190 in the United States [2]. However, to our knowledge, no published studies have assessed the average number of QALYs lost per infection or the overall annual QALY losses attributable to syphilis.

Measuring the health impact of syphilis in adults and congenital syphilis using a standard health metric like QALYs has a benefit of combining the morbidity and mortality impact into one measure [3]. Health conditions like syphilis can cause reductions in the quality and length of life, thereby reducing the number of QALYs that would have been achieved in the absence of syphilis. For example, in adults, early stage of syphilis involves symptoms like sores, skin rashes, fever, and fatigue. Development of tertiary syphilis can affect multiple organ systems such as cardiovascular and neurologic systems [4]. Clinical manifestations of congenital syphilis include rhinitis, periostitis or osteochondritis, hepatitis, pneumonitis, meningitis, hematologic derangements, as well as rash, fever, and failure to thrive, all of which can reduce quality of life in affected infants [5]. Assessing the burden of syphilis in terms of QALYs also allows for comparing the burden of syphilis with that of other health outcomes.

The purpose of our study was to estimate the average number of QALYs lost per infection and the total number of QALYs lost due to syphilis acquired in the United States in 2018 by using a Markov model that simulates long-term sequelae of syphilis infection.

METHODS

Model Overview

Our Markov model consists of 2 parts: the natural history and clinical management of syphilis. The model was run for 3 subpopulations: men who have sex with men (MSM), men who have sex with women (MSW), and women. We estimated health loss due to congenital syphilis in a separate decision tree. As primary outcomes, we estimated the lifetime QALYs lost per infection and the expected lifetime QALYs lost due to syphilis acquired in 2018.

Disease Progression

For syphilis natural history, we adopted the framework used in Tuite and colleagues [6]. The Markov cohort model consists of the following main health states in the natural history of syphilis in adults: primary, secondary, early latent, late latent, untreated tertiary, treated (no long-term sequelae), treated with long-term sequelae, neurosyphilis, and death due to syphilis or all other causes (Figure 1). Simulation begins at infection and we assumed every infected person progresses to the primary syphilis stage. If untreated, those with primary syphilis are at risk of progressing further to secondary, early and late latent, and tertiary syphilis. Monthly progression rates between primary, secondary, early latent, and late latent syphilis were determined by the duration estimates for each state [6–9]. As is conventional, the transitions in the model are exponentially distributed.

In the model, 33% of untreated syphilis has the invasion of central nervous system from treponemes ('neurologic involvement') every month (not shown in Figure 1) [10–12]. Among those with neurologic involvement, the risk of developing neurosyphilis depends on the stage of syphilis: in early syphilis (primary, secondary, and early latent), the monthly risk is 5% [6, 13]. In late latent syphilis, the 15-year risk of developing neurosyphilis is 9% (ie, 0.05% monthly risk) [6]. With high prevalence of symptomatic early neurosyphilis, we assumed that all early neurosyphilis is symptomatic [4, 10]. Although 18% of those in the early neurosyphilis state are treated every month, the rest will remain in early neurosyphilis or progress to tertiary syphilis until the next cycle starts [13, 14]. All states have a background risk of death based on age-specific all-cause mortality in the United States [15]. People with untreated tertiary syphilis have an increased probability of death, which we approximated in our model based on excess mortality in the absence of treatment [10] combined with the probability that syphilis remains untreated long enough to develop tertiary syphilis (Supplementary Appendix 1, Supplementary Figures 1 and 2). In order to calculate the number of lifetime QALYs lost attributed to both morbidity and mortality of syphilis, we calculated the difference in the quality-adjusted life expectancy for people with syphilis and for people without syphilis. We present model input parameters and their distributions in Table 1.

Testing and Treatment

Due to lack of empirical data, we used the annual rate of testing and treatment by syphilis stage and subpopulation as assumed in a previously published modeling study [14]. We summed the annual rate of seeking treatment and the rate of opportunistic screening and treatment to reflect the different routes of getting tested and treatment (eg, background screening, or treatment seeking due to symptoms). The ranges adopted reflect the considerable uncertainty in testing and treatment frequency (Table 1). Women in pregnancy have access to testing and treatment for syphilis as part of prenatal care, and we calculated the probability of testing and treatment in women by taking average between pregnant and non-pregnant women [11] (Supplementary Table 4). We assumed that sensitivity and specificity of testing is perfect, because a sequence of initial test in combination with a confirmatory test can achieve high test performance [12]. People treated for syphilis after developing late neurosyphilis or tertiary syphilis would have a lifelong residual health loss.

Disutility of Syphilis

We calculated the lifetime loss in QALYs by assuming that each state of syphilis in the Markov model was associated with a detriment in quality of life. The magnitude of this detriment, "disutility weight," was obtained from the literature (Table 1) [6, 18–20]. Utility value at a specific stage of syphilis was further adjusted by age-specific background utility [21] (Supplementary Appendix 2). We did not include the impact of stigma from syphilis on quality of life, because the disutility of stigma is hard to quantify and has typically not been included in quality-of-life weights for curable sexually transmitted infections (STIs) [20]. We calculated both undiscounted and discounted (3% annual discounting rate) QALYs lost.

Congenital Syphilis

We set a separate decision tree structure to calculate the average QALYs lost associated with congenital syphilis (Figure 2). The decision tree divides a case of congenital syphilis into 3 pregnancy outcomes: (1) live-born infants with signs or symptoms of congenital syphilis, (2) live-born infants without signs or symptoms of congenital syphilis, and (3) infants who are stillborn or born alive then die (neonatal death). In the model, 33.2%, 60.3%, and 6.0% of congenital syphilis diagnoses are live-born and symptomatic, live-born and asymptomatic, and
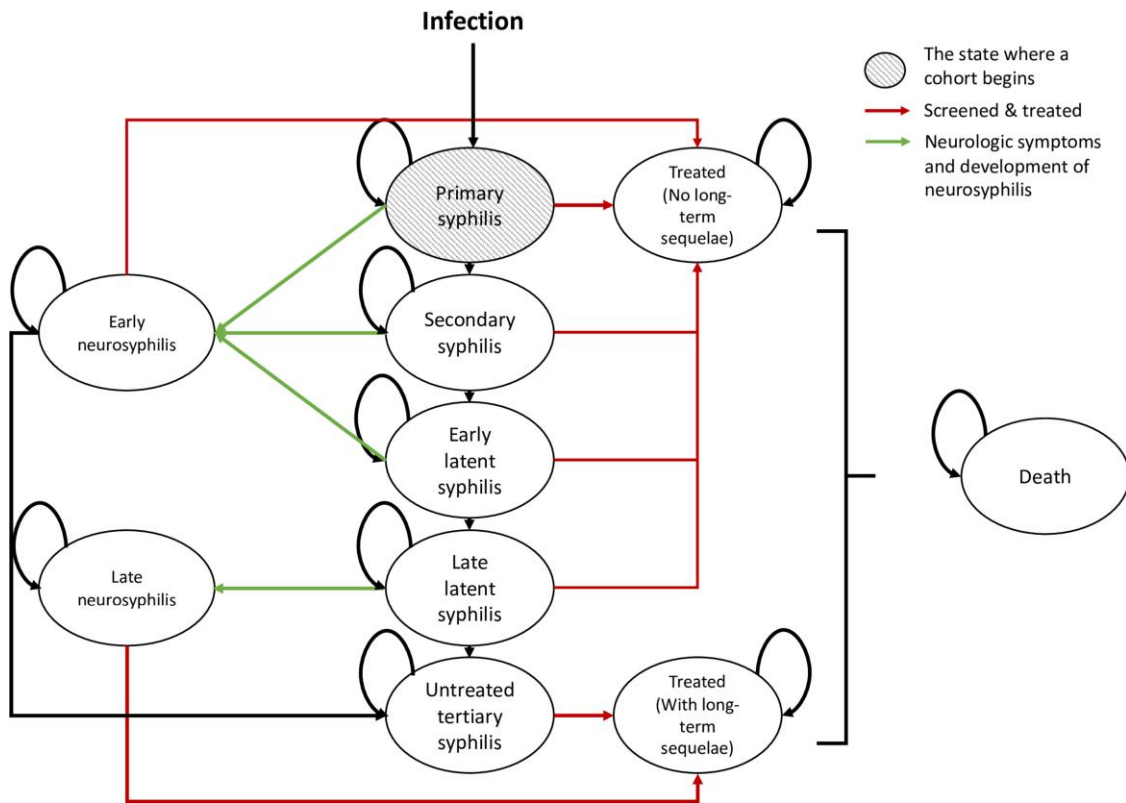
Figure 1. Markov model of syphilis. In our model, tertiary syphilis refers to gummas, cardiovascular syphilis, psychiatric manifestations, and so forth; we included late neurosyphilis as a separate outcome. Black arrows indicate health transitions in the natural history of syphilis. Neurologic symptoms and neurosyphilis can develop at any stage of syphilis (green arrows). Treatment can occur at any stage of syphilis (red arrows show the transition to the "treated" state). Reductions in quality of life attributable to syphilis are incurred at every state in this model, except early latent syphilis and late latent syphilis.

stillborn, respectively [24]. Among infants who are live-born with signs and symptoms of congenital syphilis, 27% have low birth weight, and the rest have other symptoms such as condyloma lata, snuffles, syphilitic rash, and hepatosplenomegaly [25]. In the model, live-born infants with and without signs and symptoms of disease are treated with penicillin for the first 10 days of life and do not incur a long-term reduction in quality of life [28, 29]. We assumed live-born symptomatic babies would experience symptoms for one month, whereas live-born asymptomatic babies would not have any reductions in quality of life [26]. We accounted for lifetime health losses among stillborn infants with the total discounted quality-adjusted life expectancy that was calculated based on the all-cause mortality and age-specific utility scores in the US population [15, 21]. We also estimated discounted and undiscounted QALYs lost among mothers per case of congenital syphilis. In the model, mothers with babies with congenital syphilis or low birth weight have short-term associated disutility, whereas disutility among mothers due to stillbirth lasts for 7 months [27]. Further details are in Supplementary Appendix 2.

To aggregate the number of QALYs lost due to congenital syphilis, we multiplied the number of reported congenital syphilis cases

in 2018 [30] with the estimated number of QALYs lost in children and mothers per case of congenital syphilis.

Average Number of Lifetime QALYs Lost per Infection in Subpopulations and in Total Population

In each subpopulation, we averaged the age-specific estimates of QALYs lost based on the age distribution of syphilis diagnoses in 2018 [30, 31]. In the male subpopulations (MSM, MSW), we calculated the average estimates between MSM and MSW based on the proportion of syphilis diagnoses in men attributed to MSM (78%) and MSW (22%) [30]. The average number of QALYs lost per infection in women did not include the possible QALY losses due to congenital syphilis. In the total population, we averaged the subpopulation-specific QALYs lost per infection based on the proportion of syphilis attributed to each subgroup. We provided details on the weights by age and subgroup used to calculate the average number of lifetime QALYs lost in Supplementary Appendix 3.

Total Expected Number of QALYs Lost due to Syphilis Acquired in 2018

We multiplied the estimated number of QALYs lost per infection with the total number of infections in each subpopulation

Table 1. Model Parameters Used to Estimate the Lifetime Number of Quality-Adjusted Life Years (QALYs) Lost due to Syphilis: Base Case Values, Distributions Applied in Sensitivity Analyses, and References

Variable	Base Case Value [Uncertainty Range[a]]	Distribution Type	Reference
Natural history			
Average duration of infection stage (months)			
Primary ("dur_p")	0.7 [0.25–1.96]	Lognormal (−0.36, 0.53)	[6–9]
Secondary ("dur_s")	3.6 [2.16–5.99]	Lognormal (1.3, 0.26)	[6–9]
Early latent	7.7 [3–11.4]	12 – dur_p – dur_s	[6–9]
Monthly probability of developing neurosyphilis			
In early syphilis (to early neurosyphilis)	0.017	p_neuro*pNS_early	[6, 9, 13]
In late syphilis (to late neurosyphilis)	0.00017	p_neuro*pNS_late	[6, 8, 9, 13]
Monthly probability of neurologic involvement ("p_neuro")	0.33 [0.06–0.6]	Beta (3.5, 7.1)	[6, 9, 13]
Monthly probability of progressing from early syphilis to early neurosyphilis given neurologic involvement ("pNS_early")	0.05 [0.01–0.09]	Beta (5.7, 107.4)	[6, 13]
Monthly probability of progressing from late syphilis to late neurosyphilis given neurologic involvement ("pNS_late")	0.0005 [0.0003–0.0007]	Supplementary Table 1	[6]
Monthly probability of recovery from early neurosyphilis through treatment	0.18 [0.12–0.28]	Supplementary Table 1	[6, 16]
Monthly probability of progressing from early neurosyphilis or late latent to tertiary syphilis	0.0012 [0.008–0.02]	Supplementary Table 1	[6, 8]
Monthly probability of treatment failure			
Primary, secondary, early latent	0.05 [0–0.1]	Beta (3.6, 68.4)	[6]
Late syphilis (latent syphilis)	0.19 [0.08–0.3]	Beta (9.1, 38.8)	[6]
Mortality			
All-cause among untreated tertiary syphilis	Supplementary Table 2[b]	Fixed	[17]
All-cause in other health states	Age- and sex-specific mortality in the US	Fixed	[15]
Disutility of syphilis			
Primary ("du_p")	0.006 [0.004–0.01]	Beta (3.8, 631.6)	[6, 18]
Secondary ("du_s")	0.04 [0.02–0.06]	Beta (14.7, 343.7)	[6, 18]
Early latent ("du_el")	0	Fixed	[6, 18]
Late latent	0	Fixed	[6, 18]
Early neurosyphilis	0.05 [0.03–0.08]	Beta (14.5, 276.4)	[19]
Late neurosyphilis	0.20 [0.12–0.29]	Beta (16.5, 64.6)	[20]
Tertiary syphilis (cardiovascular/gummatous)	0.24 [0.15–0.33]	Beta (21.0, 65.3)	[20]
Long-term disutility of tertiary and late neurosyphilis syphilis following treatment	0.09 [0.05–0.14]	Beta (13.8, 133.3)	[6, 18]
Background utility	Supplementary Table 3	Fixed	[21]
Annual rate of testing and treatment			
Primary (MSW)	0.30 [0–0.65]	Beta (1.7, 3.9)	[14]
Secondary (MSW)	0.51 [0.16–0.86]	Beta (3.5, 3.4)	[14]
Early latent (MSW)	0.30 [0–0.65]	Beta (1.7, 3.9)	[14]
Late latent (MSW)	0.19 [0–0.47]	Beta (1.2, 5.3)	[14]
Primary (MSM)	0.55 [0.1–1]	Beta (2.0, 1.7)	[14]
Secondary (MSM)	0.76 [0.42–1]	Beta (3.8, 1.2)	[14]
Early latent (MSM)	0.44 [0.01–0.87]	Beta (1.8, 2.3)	[14]
Late latent (MSM)	0.44 [0.01–0.87]	Beta (1.8, 2.3)	[14]
Primary (Non-pregnant women)[c]	0.30 [0–0.65]	Beta (1.7, 3.9)	[14]
Secondary (Non-pregnant women)	0.51 [0.16–0.86]	Beta (3.5, 3.4)	[14]
Early latent (Non-pregnant women)	0.30 [0–0.65]	Beta (1.7, 3.9)	[14]
Late latent (Non-pregnant women)	0.19 [0–0.47]	Beta (1.2, 5.3)	[14]
Primary (Pregnant women)[c]	0.79 [0.46–1]	Beta (3.8, 1.0)	[22, 23]
Secondary (Pregnant women)	0.79 [0.46–1]	Beta (3.8, 1.0)	[22, 23]
Early latent (Pregnant women)	0.79 [0.46–1]	Beta (3.8, 1.0)	[22, 23]
Late latent (Pregnant women)	0.79 [0.46–1]	Beta (3.8, 1.0)	[22, 23]
Percentage of congenital syphilis diagnoses with clinical characteristics of infants (%)			
Live-born with signs or symptoms of congenital syphilis	33.20 [30.4–35.6]	Dirichlet (431, 796.7, 78.3)	[24]

Table 1. Continued

Variable	Base Case Value [Uncertainty Range[a]]	Distribution Type	Reference
Live-born with no signs or symptoms of congenital syphilis	60.30 [58.3–63.6]	Dirichlet (431, 796.7, 78.3)	[24]
Stillborn	6.50 [4.78–7.33]	Dirichlet (431, 796.7, 78.3)	[24]
Percentage of symptomatic congenital syphilis with infant outcomes (%)			
Low birth weight ("pCS_LB")	27 [24.6–29.5]	Dirichlet (352.6, 953.3)	[25][d], expert opinion
Other congenital syphilis symptoms	73 [70.5–75.4]	1-'pCS_LB'	[25][d], expert opinion
Disutility of mothers due to adverse pregnancy outcomes			
Stillbirth	0.08 [0–0.2]	Beta (1.5, 17.1)	[26]
Congenital syphilis	0.12 [0–0.3]	Beta (1.4, 10.1)	[26]
Low birth weight	0.0001 [0–0.005]	Beta (0.000006, 0.11)	Assumed
Duration of disutility in mother who lost a child	7 months	Fixed	[27]
Disutility of babies due to adverse pregnancy outcomes			
Symptoms of congenital syphilis other than low birth weight	0.26 [0.12–0.4]	Beta (9.5, 27.2)	[26]
Low birth weight	0.11 [0.05–0.16]	Beta (12.1, 102.9)	[26]
Total number of QALYs lost to the unborn child per instance of stillbirth	28.50	Fixed	[15, 21] Calculated, Supplementary Appendix 2
Total number of undiscounted QALYs lost to the unborn child per instance of stillbirth	70.00	Fixed	[15, 21] Calculated, Supplementary Appendix 2
State transition cycle	1 month	Fixed	Assumed
Annual discount rate	0.03	Fixed	Assumed

Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women.

[a]The method to set up uncertainty range is provided in Supplementary Appendix 4.

[b]We applied age-specific hazard rate ratios of mortality with untreated syphilis to the baseline all-cause mortality to calculate all-cause mortality among those with tertiary syphilis. Details on the calculation of the age-specific hazard rate ratios of mortality with untreated syphilis is provided in Supplementary Appendix 1.

[c]See Supplementary Table 4 for the calculation of average testing and treatment rate among women.

[d]The estimate for the proportion of low birth weight among liveborn babies in the reference was adjusted based on the author assumption.

or in the total population. We used the estimated incidence of syphilis in people aged 15–49 years in 2018 [31]. Further details are provided in Supplementary Appendix 3.

Uncertainty Analysis

We performed probabilistic sensitivity analysis to generate ranges around the model's estimates given the significant uncertainty in the model's input parameters including natural history parameters, probability of screening and treatment in different subpopulations, and the disutility associated with the adverse outcomes (Table 1). The 2.5th and 97.5th percentiles of results from the 1000 sampled parameter sets are presented as the 95% uncertainty intervals. The distributions used in the sensitivity analysis are described in Supplementary Appendix 4.

RESULTS

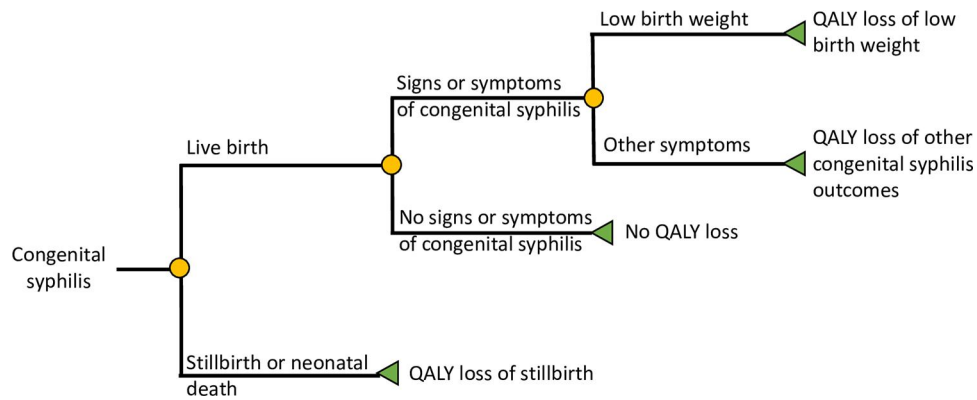### Number of QALYs Lost per Infection by Age at Primary Infection

The number of QALYs lost due to syphilis per infection varied by age at infection (Figure 3, Supplementary Tables 5 and 6). In all subpopulations, the number of QALYs lost per infection decreased with age at infection. The number of QALYs lost per infection was about 25%–60% lower for MSM than for MSW and women, primarily due to the higher testing and

treatment rates in MSM. With primary infection at the ages 20–24 years, for example, the discounted lifetime number of QALYs lost per infection among MSM was 0.07 (95% UI .02–.21), whereas the number of QALYs lost per infection among MSW and women was 0.17 (95% UI .04–.45) and 0.09 (95% UI .04–.20), respectively. Women had lower QALYs lost per infection during the reproductive ages (15–39 years) when pregnant women have increased testing and treatment during pregnancy.

Without discounting, the number of QALYs lost per infection ranged between 0.05 and 0.53. For example, when primary infection occurred at the ages 20–24 years, the undiscounted lifetime number of QALYs lost per infection among MSM was 0.15 (95% UI .03–.55), whereas in MSW and women the estimates were 0.43 (95% UI .09–1.32) and 0.21 (95% UI .07–.49), respectively.

Average Lifetime Number of QALYs Lost per Infection via Adult Subpopulations and Total Population

The average number of QALYs lost due to syphilis per infection among MSM was lower than in MSW and women (Figure 4A, Supplementary Table 7). On average, the discounted number of QALYs lost per infection was 0.06 (95% UI .02–.19) in MSM, whereas it was 0.15 (95% UI .04–.3) and 0.10 (95% UI .04–.23) in MSW and women, respectively. In the entire US

Figure 2. Decision tree model used to estimate the number of quality-adjusted life years (QALYs) lost due to congenital syphilis.

population, the average discounted number of QALYs lost per infection was 0.09 (95% UI .03–.19). The undiscounted number of QALYs lost per infection was 0.12 (95% UI .03–.43) in MSM, whereas it was 0.33 (95% UI .07–.97) and 0.22 (95% UI .07–.54) in MSW and women, respectively (Figure 4B, Supplementary Table 7). In the entire US population, the average undiscounted number of QALYs lost per infection was 0.18 (95% UI .06–.43).

Total Lifetime Number of QALYs Lost due to Syphilis Acquired in 2018
In total, syphilis incidence in 2018 was expected to result in 13 349 discounted QALYs lost (95% UI 5071–31 360) in the US population (Figure 4C). MSM account for 47.7% of the total

number of discounted QALYs lost (6373 QALYs lost). MSW and women account for 32.1% (4286 QALYs lost) and 20.2% (2691 QALYs lost) of the total number of discounted QALYs lost, respectively.

When future health loss was not discounted, the total number of QALYs lost due to syphilis in 2018 was estimated to be 27 544 (95% UI 8446–71 594) (Figure 4D). The expected total number of QALYs lost due to syphilis in 2018 in MSM, MSW, and women was 12 276, 9546, and 5722 respectively. Mean estimate and uncertainty range of the total number of QALYs lost are described in Appendix (Supplementary Table 8). In total, all syphilis incidence that was sexually and vertically acquired in 2018 is expected to cause 13 349 QALYs
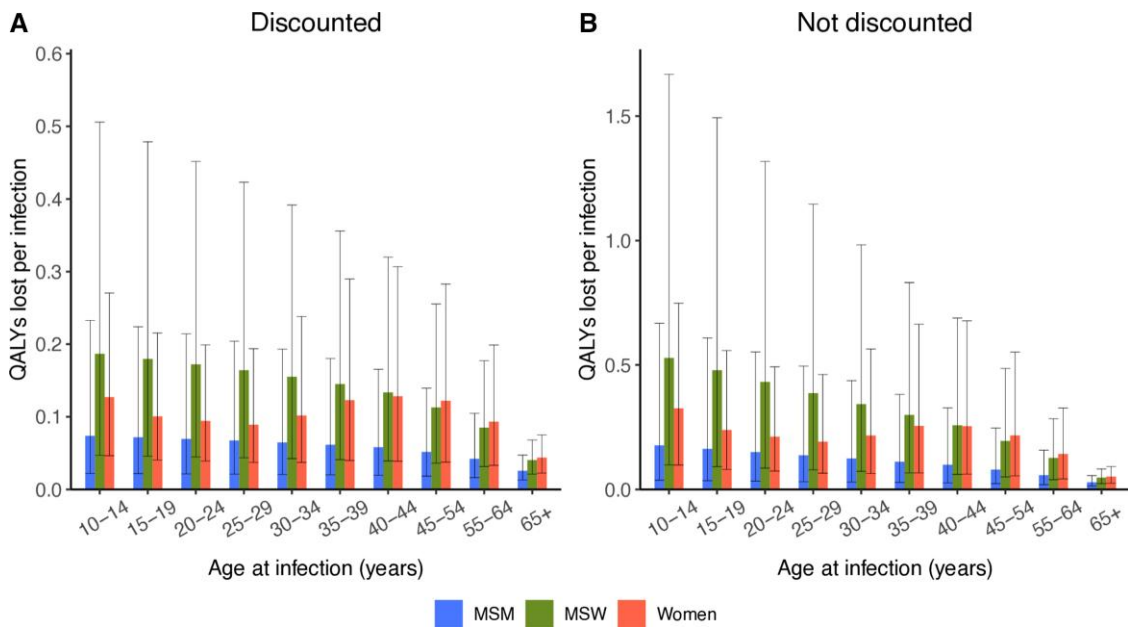
Figure 3. Lifetime number of QALYs lost due to syphilis (per infection) by age at infection for men who have sex with men (MSM), men who have sex with women (MSW), and women: (A) discounted number of QALYs lost per infection; (B) undiscounted number of QALYs lost per infection. The error bars shown reflect the 2.5th and 97.5 percentiles of results from the sensitivity analyses. Abbreviation: QALY, quality-adjusted life year.
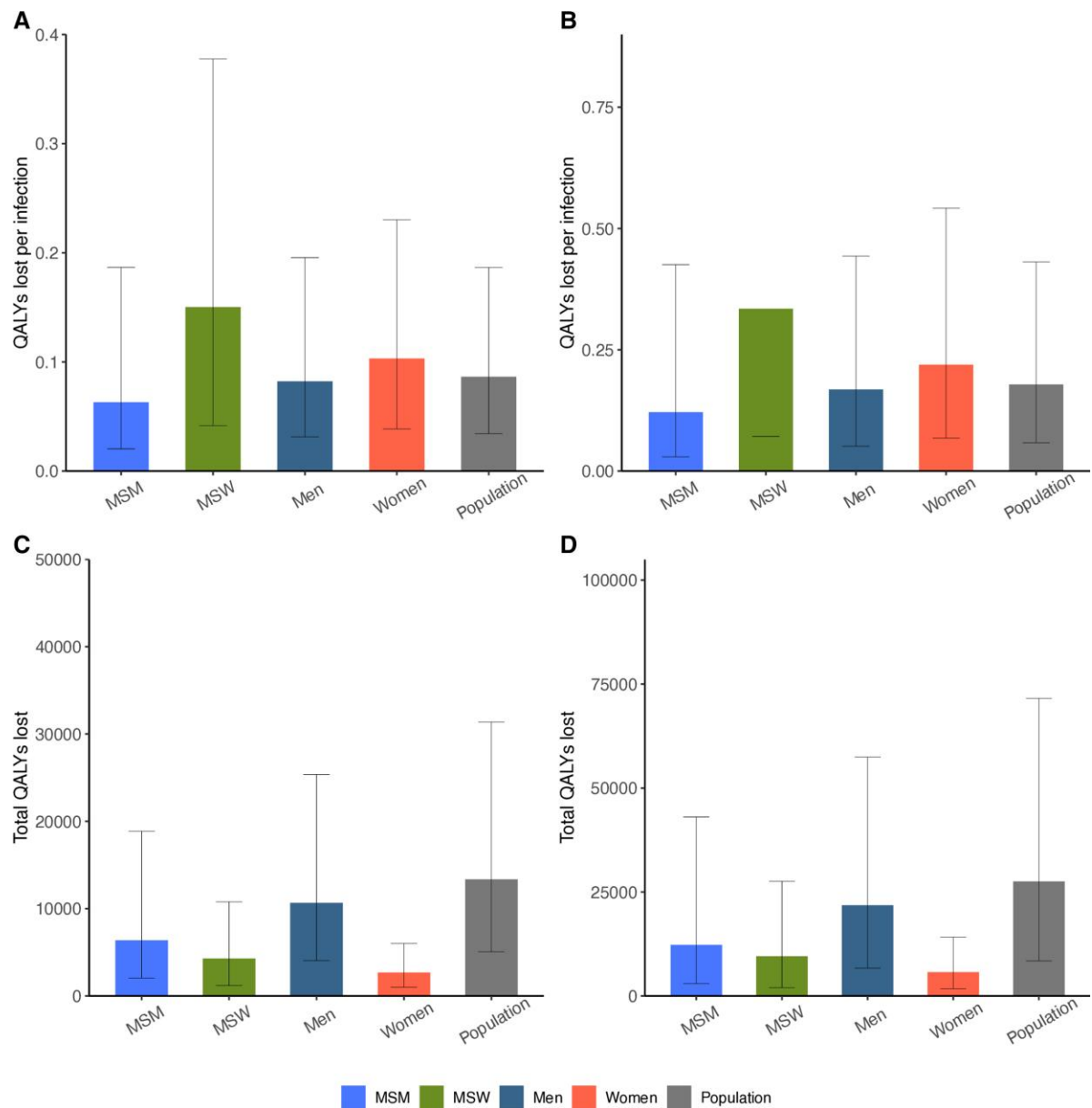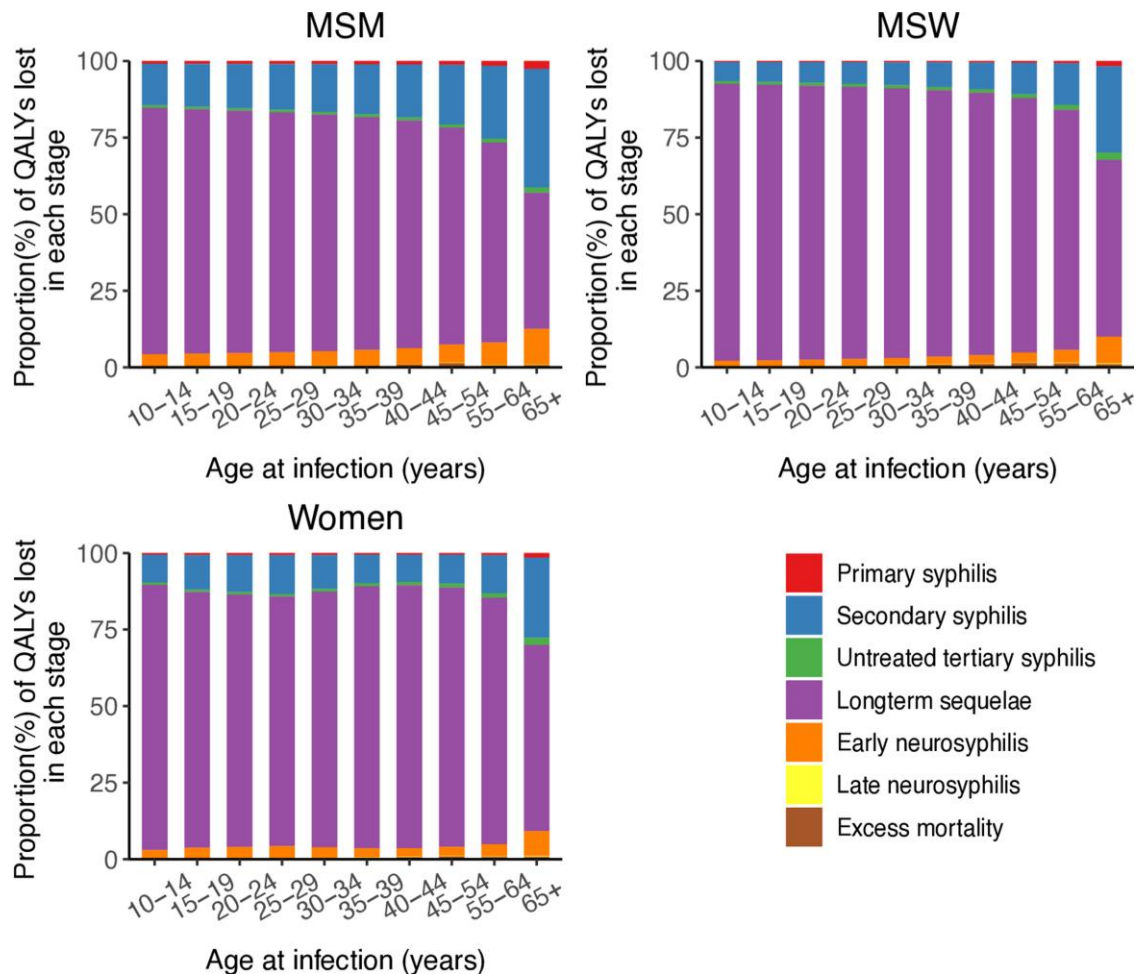
Figure 4. Average lifetime number of QALYs lost due to syphilis (per infection) and total number of QALYs lost due to syphilis acquired in 2018 for men who have sex with men (MSM), men who have sex with women (MSW), women, and total population: (*A*) discounted QALYs lost per infection; (*B*) undiscounted QALYs per infection; (*C*) discounted total QALYs lost; (*D*) undiscounted total QALYs lost. The error bars shown reflect the 2.5th and 97.5 percentiles of results from the sensitivity analyses.

lost if the estimate is discounted, and 27 544 QALYs lost if the estimate is not discounted.

Disutility from long-term sequelae with late neurosyphilis or tertiary syphilis accounted for the largest proportion of the estimated total number of QALYs lost (Figure 5). Compared to MSW and women, a lower proportion of the QALY burden in MSM was attributable to late syphilis (untreated tertiary syphilis, late neurosyphilis, and their long-term sequalae). In all subpopulations, the proportion of QALYs lost due to excess mortality with syphilis was relatively low.

QALYs Lost due to Congenital Syphilis

On average, each case of congenital syphilis resulted in a loss of 0.06 QALYs (95% UI .01–.14) in mothers and 1.79 QALYs (95% UI 1.43–2.16) in the affected child (Figure 6A, Supplementary Table 9). If future health loss was not discounted, the value would be 0.06 and 4.28 for mothers and children, respectively. The total number of lifetime QALYs lost due to congenital syphilis cases that occurred in 2018 was 79.49 for mothers and 2332 for children (Figure 6B). Without discounting, the total expected number of QALYs lost for mothers and

Figure 5. Proportion of the number of QALYs lost attributed to each stage of syphilis for men who have sex with men (MSM), men who have sex with women (MSW), and women. Abbreviation: QALY, quality-adjusted life year.

children is 84 and 5596, respectively. We provided the number of QALYs lost per infection in women with and without including QALY losses due to congenital syphilis in Supplementary Table 10.

DISCUSSION

We quantified the lifetime number of QALYs lost due to syphilis per infection in the US population. Our findings have 2 key public health implications. First, syphilis screening can prevent sequelae and thereby reduce the impact of syphilis on quality of life. Specifically, the number of QALYs lost per infection is lower in MSM than in MSW because MSM have higher rates of screening and treatment. For example, the Centers for Disease Control and Prevention (CDC) guidelines recommend annual syphilis serology test for sexually active MSM, including those with human immunodeficiency virus (HIV) infection [32]. Second, congenital syphilis has a dramatic impact on morbidity and mortality. The number of QALYs lost to infants per

case of congenital syphilis far exceeds the number of QALYs lost per infection in adults. Lack of engagement in antenatal care and inadequate syphilis screening and treatment during antenatal care leads to a higher risk of congenital syphilis and consequent health losses both in children and mothers [24]. The burden of congenital syphilis is even higher among women with limited access to antenatal care and treatment for syphilis [33, 34].

Our results can inform cost-effectiveness analyses of syphilis prevention interventions with existing estimate of lifetime medical cost per infection [3]. We note that previous estimates of the lifetime number of QALYs lost per HIV infection [35] have been used in a similar manner in numerous cost-effectiveness analyses of HIV prevention interventions [36–38].Our results can also help to quantify the health burden of syphilis and facilitate comparison to other adverse health outcomes. For example, the average lifetime number of QALYs lost per infection that we estimated (0.09 QALYs) can be compared to 5.8 QALYs lost per HIV infection [35, 38]
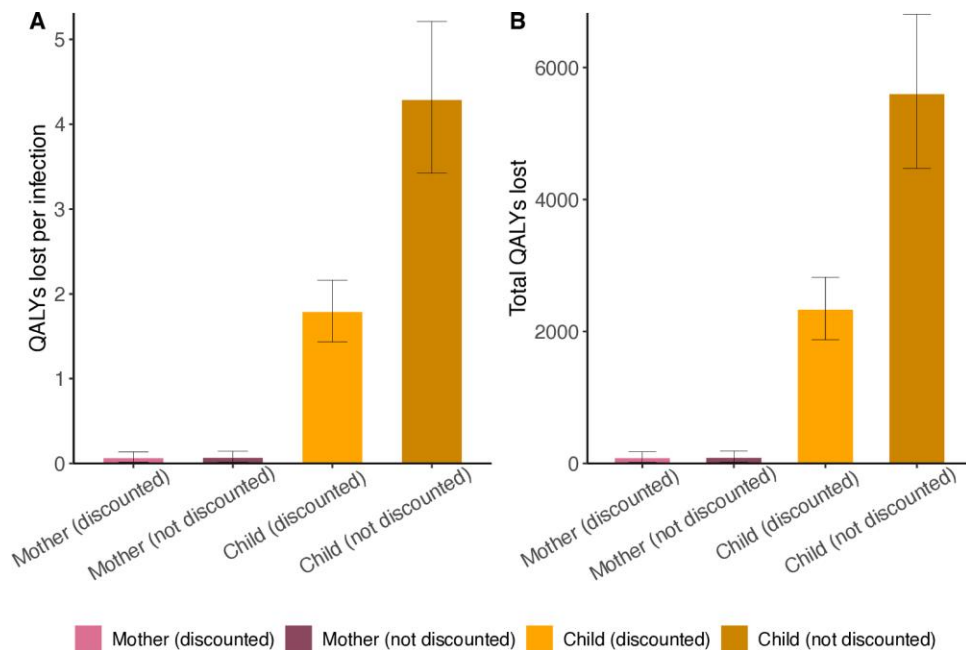
Figure 6. Number of QALYs lost due to congenital syphilis: (*A*) Average number of QALYs lost per case of congenital syphilis; (*B*) total expected number of QALYs lost due to congenital syphilis cases that occurred in 2018. The error bars shown reflect the 2.5th and 97.5 percentiles of results from the sensitivity analyses. Abbreviation: QALY, quality-adjusted life year.

and 0.024 QALYs lost per case of genital warts [39–41]. Similarly, our estimate of the total number of QALYs lost due to syphilis acquired in 2018 (13 349 QALYs) can be compared to estimates of the total number of QALYs lost due to other infections.

Our study illustrates the challenges associated with estimating the lifetime QALY loss due to syphilis. Limited data exist to inform treatment rates, progression rate, and disutility of syphilis of adverse outcomes of syphilis. We accounted for the uncertainty in treatment rates and in other model inputs by performing sensitivity analyses with a wide uncertainty range. Our analysis can be further updated as better data become available. There is currently no consensus on how long the parental QALYs losses from losing a child should be counted [42–44]. Using an intermediate approach to include a temporary disutility for mothers who lost a child, our estimate on lifetime health loss due to congenital syphilis among mothers would be lower than the estimate when lifelong disutility of losing a child is considered and lower than when parental effects are completely excluded. The scope of our study can be further extended to account for health losses such as loss of visual acuity due to ocular syphilis, given that ocular manifestations have increased among the reported syphilis cases [45]. Although our study focused on health losses directly associated with sequelae following infection, including other possible health outcomes associated with syphilis, such as new HIV infections attributable to the facilitative effects of syphilis on HIV transmission

and acquisition, can increase our estimate of health losses due to syphilis.

In summary, we developed estimates of the quality-of-life impact of adult syphilis and congenital syphilis in the United States. Our estimates can be used in a wide range of health economic studies and burden of disease studies of syphilis. Finally, we provided detailed documentation of our methods and assumptions so that those who use our estimates in future studies can make updates and modifications as needed in their application of our estimates.

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

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