Appendix: The Estimated Lifetime Medical Cost of Syphilis in the United States

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Appendix Table A-1: Calculation of probability that those infected but not reported as syphilis cases would be alive and still infected 30 years after infection

Item estimated	Estimate	Data sources and other notes
Average annual number of reported cases, 1969 through 1987	77,000	In our base case, we assumed 30 years from infection to onset of sequelae of late syphilis. Under this assumption, syphilis incidence in the 19-year period 1969-1987 corresponds to late syphilis outcomes in the 19-year period 1999-2017. Reported case numbers were obtained from STD surveillance data.[1]
Estimated average annual number of infections from 1969 through 1987 that are never reported as cases	19,250	In our base case, we assume 80% of infections are eventually reported as cases.[2-4]
Average annual number of reported deaths due to late syphilis, 1999 through 2017	37	Data on late syphilis deaths was obtained from CDC wonder. https://wonder.cdc.gov/
Probability that late syphilis is listed as cause of death, given that death is attributable to late syphilis	0.5	Based on a study indicating that 51% of death certificates had major errors such as major comorbidities/contributing causes absent or wrong, or wrong underlying cause.[5]
Estimated annual number of late syphilis deaths, adjusted for under-reporting on death certificates, 1999 through 2017	74	Calculated from two preceding rows (37 divided by 0.5).
Probability of death attributable to syphilis among those with severe complications of syphilis	0.73	In a review of six studies totaling 39,907 autopsies, 73% of deaths (range 51% to 87%) among those with morphologic changes recognized as syphilitic at autopsy were attributed primarily to syphilis.[6] We note that this probability of death attributable to syphilis is applicable only to those with severe complications of syphilis, which in our model are cardiovascular syphilis, meningovascular syphilis, tabes dorsalis, and general paresis. In our model, these severe complications occur in 16% of those still alive and infected 30 years after acquiring syphilis; the remaining 84% was accounted for by latent syphilis (68%) and late benign syphilis (16%), as described below. When applying a 73% probability of death to the 16% of people with severe outcomes (cardiovascular syphilis, meningovascular syphilis, tabes dorsalis, or general paresis), the probability of death given untreated syphilis in our model would be 73% x 16% = 12%. This value closely matches the 11% (75/694) cumulative probability of dying from syphilis among those in the Oslo study of untreated syphilis, as reported by Clark and

		Danbolt.[7] We note the probability of death given untreated syphilis in our model would be lower than 12% if the denominator were expanded to include not only those still alive and infected 30 years after acquiring syphilis but also those with untreated syphilis who died an unrelated death within 30 years of acquisition, prior to the onset of late syphilis outcomes (see Outcome G of the decision tree).
Estimated annual number of cases (fatal and non-fatal) of cardiovascular syphilis, meningovascular syphilis, tabes dorsalis, and general paresis, 1999 through 2017	101.4	Calculated as 74 divided by 0.73; if there are 101.4 cases total and 73% of cases are fatal, we would expect 74 deaths.
Probability of cardiovascular syphilis, meningovascular syphilis, tabes dorsalis, or general paresis, if alive and still infected 30+ years after infection	0.16	This value of 0.16 represents the sum of the probabilities of cardiovascular syphilis, meningovascular syphilis, tabes dorsalis, or general paresis, if alive and still infected 30+ years after infection, as described in Table 1 of the main manuscript. This value was based on a previous decision tree model[8] that incorporated data from the Oslo study.[9]
Expected annual number of cases of cardiovascular syphilis, meningovascular syphilis, tabes dorsalis, or general paresis, if 100% of those infected from 1969 through 1987 and not reported as cases were alive and still infected after 30+ years	3,080	Calculated by multiplying value in preceding row (0.16) by 19,250 (the estimated annual number of infections from 1969 through 1987 that are not reported as cases, from row 2 of this table).
Probability that those infected from 1969 through 1987 and not reported as cases are alive and still infected 30+ years later	0.033	Calculated as the estimated annual number of cases of late syphilis (101.4, from three rows above) divided by 3,080 from preceding row.

The CDC Wonder mortality data was obtained from https://wonder.cdc.gov/, accessed March 27, 2020. We used the following ICD-10 Codes: A52.0 (Cardiovascular syphilis); A52.1 (Symptomatic neurosyphilis); A52.2 (Asymptomatic neurosyphilis); A52.3(Neurosyphilis, unspecified); A52.7 (Other symptomatic late syphilis); A52.8 (Late syphilis, latent); A52.9 (Late syphilis,unspecified); A53.0 (Latent syphilis, unspecified as early or late); A53.9 (Syphilis, unspecified). We included deaths in the following ten-year age groups: 25-34 years; 35-44 years; 45-54 years; 55-64 years; 65-74 years; 75-84 years; 85+ years.

To account for uncertainty in these assumptions, we applied the following ranges. We assumed the annual number of reported syphilis cases ranged from 62,000 (the average annual number of reported cases from 1989-2007, reflecting a 10-year lag between infection and late syphilis outcomes) to 97,000 (the average annual number of reported cases from 1959-1977, reflecting a 40-year lag between infection and late syphilis outcomes).[1] We assumed that the annual number of reported deaths from late syphilis ranged from 24 to 56, based on the minimum and maximum annual values in the CDC Wonder mortality data from 1999-2017. We assumed that the probability that late syphilis was listed as the cause of death (among deaths attributable to late syphilis) ranged from 0.25 to 0.75. We assumed that the probability of death due to syphilis among those with severe complications of syphilis ranged from 0.51 to 0.87, based on the range of studies reported by Rosahn.[6] For each of these parameters, we assumed a uniform distribution between the lower and upper bound values. We then estimated the probability of treatment or death prior to onset of long-term sequelae (among those infected but not reported as cases) 5,000 times, each time choosing a random value for each input (annual number of reported cases, annual number of reported deaths from late syphilis, probability that syphilis is listed as cause of death when the death is attributable to syphilis, and the probability of death due to severe complications of syphilis among those with severe complications of syphilis) from its uniform distribution. In 95% of these 5,000 simulations, the probability that those infected from 1969 through 1987 and not reported as cases would be alive and still infected 30+ years later ranged from 0.016 to 0.091, which we applied as the lower and upper bound values for this probability. To be consistent with this distribution of values, we applied a beta distribution (2.84, 83.33) for this probability in the probabilistic sensitivity analysis of the lifetime cost of syphilis per infection as noted in Table 1 of the main manuscript. In the calculations described here, we did not vary the proportion of infections that are reported as cases (0.80). Instead, we allowed this proportion to vary separately in the one-way sensitivity analysis and probabilistic sensitivity analysis as described in the main manuscript.

Appendix Table A-2: Per-unit costs (base case, lower, and upper values) of medical services applied in model

Medical service	Cost per unit		
	Base case value	Lower value	Upper value
Office visit, new patient	$163[10]	$47[11]	$245[10]
Office visit, established patient	$106[10]	$31[*]	$159[10]
Benzathine penicillin G 2.4 million units IM single dose	$326[12]	$242[12]	$438[13]
Injection	$17[14]	$13[11]	$23[14]
Blood draw	$3[15]	$2[11]	$11[11,15]
Rapid plasma reagin (RPR) test	$6[16]	$3	$7
Aqueous crystalline penicillin G 18–24 million units	$139[13]	$55	$286
Procaine penicillin G 2.4 million units	$110[12,13]	$67[12]	$159[13]
Probenecid 500 mg	$2[13]	$1	$4
Day of hospitalization	$1,891[17]	$724	$3,798
X-ray	$41[14]	$36	$55
Computed tomography (CT) scan	$335[14]	$288	$456
Lumbar puncture and cerebrospinal fluid (CSF) analysis	$319[14,18]	$90[14]	$650[18]
Fluorescent treponemal antibody absorbed (FTA-ABS) test	$24[19]	$16	$41
Venereal Disease Research Laboratory (VDRL) test	$5[20]	$3[**]	$7[*]
Echocardiogram	$487[21]	$249[22]	$753[21]
Coronary angiography and heart catheterization	$1,209[23]	$604	$2,418
Biopsy and pathologist's exam	$225[24]	$64	$541
Aortic valve replacement surgery	$46,819[25]	$12,223[***]	$104,658[***]
One year of cardiovascular syphilis follow-up services	$974[†]	$498[†]	$1,506[†]
Treatment for meningoencephalitis[¶]	$21,660	$9,913	$58,635
Treatment for stroke	$24,444[26]	$3,823[***]	$95,381[***]
One year of long-term care for meningovascular syphilis, general paresis[‡]	$32,435[27]	$23,763	$41,107
One year of tabes dorsalis follow-up services[§]	$2,409[28]	$1,443	$3,375

[*]For the office visit of an established patient, the lower bound was calculated by assuming the same ratio of the lower bound to the base case value as was applied for the office visit of a new patient.

[**]For VRDL, the range of cost values was assumed to be the same as that of RPR, which had a similar baseline value.

[***]Values for range chosen to be consistent with the standard deviation reported in the source study.

[†]Calculated assuming annual follow-up consists of two echocardiograms per year[8] and applying the unit costs in this table.

¶The cost of treatment for meningoencephalitis was calculated as the approximate average of estimated cost for patients hospitalized with meningitis and encephalitis.[29]
‡ Following Schmid and Zaidi (1995),[8] we assumed a proportion of patients with meningovascular syphilis and general paresis would require long-term care and that the annual cost of this long term-care would be similar to the annual costs of care associated with dementia.
§We assumed the annual costs associated with tabes dorsalis would be at least as much as the annual costs associated with arthritis. Common symptoms of tabes dorsalis include lighting pains, lack of muscle control or coordination, paresthesias, weakness, and progressive degeneration of the joints (https://www.ninds.nih.gov/Disorders/All-Disorders/Tabes-Dorsalis-Information-Page, accessed March 5, 2020).[30]

Costs updated to 2019 dollars using the personal consumption expenditures price index for health care. Except where noted, when no source is listed for a lower bound or upper bound value, the source was the same as listed for the base case value.

Appendix Table A-3: Resources required, per person treated for primary and secondary (P&S) and early non-P&S syphilis

Item	Resources required, all patients	Additional resources required by those patients who receive follow-up
Office visit, new patient	1	
Office visit, established patient	0.5	2
Benzathine penicillin G 2.4 million units IM single dose	1	
Injection	1	
Blood draw	1	2
RPR (rapid plasma reagin) test	1	2
Fluorescent treponemal antibody absorbed (FTA-ABS) test	1	

Appendix Tables A-3 through A-10 were based on Schmid and Zaidi (1995).[8] For the assumptions attributed to the Schmid and Zaidi model[8] in these tables and elsewhere in this appendix and the main manuscript, details of their model were obtained from an unpublished manuscript "Screening for syphilis: Preliminary results of a decision tree and economic analysis" acquired from George Schmid circa 1997. We incorporated 0.5 office visits for established patients under the assumption that some patients with syphilis might require a repeat visit for treatment.

Appendix Table A-4: Resources required, per person treated for syphilis of unknown duration or for late syphilis

Item	Resources required, all patients	Additional resources required by those patients who receive follow-up
Office visit, new patient	1	
Office visit, established patient	2	3
Benzathine penicillin G 2.4 million units IM single dose	3	
Injection	3	
Blood draw	1	3
RPR (rapid plasma reagin) test	1	3
Fluorescent treponemal antibody absorbed (FTA-ABS) test	1	

As noted in Table A-11, we allowed for the possibility that some patients might also receive a lumbar puncture and CSF analysis.

Appendix Table A-5: Additional resources required for patients treated for neurosyphilis or ocular syphilis

Item	**Resources required by patients treated with Aqueous crystalline penicillin G**	**Resources required by patients treated with procaine penicillin G plus probenecid**
Aqueous crystalline penicillin G 18–24 million units	10 to 14	0
Procaine penicillin G 2.4 million units	0	10 to 14
Probenecid 500 mg	0	40 to 56
Injection	0	10 to 14
Fluorescent treponemal antibody absorbed (FTA-ABS) test	1	1
Venereal Disease Research Laboratory (VDRL) test	1	1
Lumbar puncture and cerebrospinal fluid (CSF) analysis	1	1
Day of hospitalization	10 to 14	0
Office visit, new patient		1
Office visit, established patient		9 to 13

These resource requirements are in addition to those required for treatment at P&S, early non-P&S, unknown duration or late stage. When a range is provided, these values represent the lower bound and upper bound values applied. In the base case, the midpoint was applied. For example, for patients in the first column, 12 days of hospitalization were assumed when estimating the base case value of the cost of neurosyphilis, 10 days were assumed when estimating the lower bound value, and 14 days were assumed when estimating the upper bound value.

Appendix Table A-6: Resources required for those treated for late benign syphilis

Item	**Resources required, all patients**
Office visit, new patient	1
Office visit, established patient	4
Benzathine penicillin G 2.4 million units IM single dose	3
Injection	3
Blood draw	2
RPR (rapid plasma reagin) test	2
Biopsy and pathologist's exam	1
X-ray	3
CT scan	2
Lumbar puncture and cerebrospinal fluid (CSF) analysis	1
Fluorescent treponemal antibody absorbed (FTA-ABS) test	1
Venereal Disease Research Laboratory (VDRL) test	1

Appendix Table A-7: Resources required for those treated for cardiovascular syphilis

Item	**Resources required by patients who do not have cardiac surgery**	**Resources required by patients who have cardiac surgery**
Office visit, new patient	3	3
Office visit, established patient	2	2
Benzathine penicillin G 2.4 million units IM single dose	3	3
Injection	3	3
Blood draw	2	2
RPR (rapid plasma reagin) test	2	2
Biopsy and pathologist's exam	1	1
X-ray	1	1
Echocardiogram	1	1
Angiography	1	1
Catheterization	1	1
Surgery for aortic valve replacement	0	1
Number of years of cardiovascular syphilis follow-up care, among those not dying from cardiovascular syphilis	22 (range: 8 to 41)	22 (range: 8 to 41)

The base case value of 22 years of follow-up care reflects the undiscounted remaining years of life expectancy when assuming a median age of infection of 31 years and when assuming 30 years from time of infection to onset of costs for cardiovascular syphilis. The lower bound value of 8 years was calculated by assuming a median age of infection of 37 years and assuming 45 years from time of infection to onset of costs. The upper bound value of 41 years was calculated by assuming a median age of infection of 25 years and assuming 15 years from time of infection to onset of costs. Life expectancy was calculated using 2015 mortality statistics,[31] available online from: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/NVSR/67_07/Table01.xlsx. The number of years of follow-up shown in this table was applied to those with cardiovascular syphilis for whom death was not attributable to cardiovascular syphilis. For the majority of patients with cardiovascular syphilis, we assumed that death would be attributable to cardiovascular syphilis (see Table A-1). For those whose death was attributable to cardiovascular syphilis, we applied one-fourth the number of years of follow-up shown in this table, under the assumption that death would occur prior to the need for follow-up among half of these patients and that death would occur at the midway point for the other half of these patients. For example, for those for whom death was attributed to cardiovascular syphilis, we assumed 5.5 years (range 2 to 10.25) of follow-up.

Appendix Table A-8: Resources required for those treated for tabes dorsalis

Item	Resources required, all patients
Office visit, new patient	2
Lumbar puncture and cerebrospinal fluid (CSF) analysis	1
Day of hospitalization	10
Aqueous crystalline penicillin G 18–24 million units	10
Blood draw	2
RPR (rapid plasma reagin) test	2
Number of years of tabes dorsalis follow-up care, among those not dying from tabes dorsalis	22 (range: 8 to 41)

See Appendix Table A-7 for a description of the estimated number of years of follow-up care required. The values shown are the undiscounted number of years. The number of years of follow-up shown in this table was applied to those with tabes dorsalis for whom death was not attributable to tabes dorsalis. For the majority of patients with tabes dorsalis, we assumed that death would be attributable to tabes dorsalis (see Table A-1). For those whose death was attributable to tabes dorsalis, we applied one-fourth the number of years of follow-up shown in this table.

Appendix Table A-9: Resources required for those treated for meningovascular syphilis

Item	**Resources required by patients who do not have stroke**	**Resources required by patients who have stroke**
Office visit, new patient	1	1
Lumbar puncture and cerebrospinal fluid (CSF) analysis	1	1
Day of hospitalization	10	10
Aqueous crystalline penicillin G 18–24 million units	10	10
Blood draw	2	2
RPR (rapid plasma reagin) test	2	2
Treatment for meningoencephalitis	1	0
Treatment for stroke	0	1
Number of years of long-term care among those not dying from meningovascular syphilis	0	83% require 0, 17% require 22 (range: 8 to 41)

We applied a 75% probability of stroke among patients with meningovascular syphilis (see Table A-11). The number of years of long-term care shown in this table among those treated for meningovascular syphilis who have stroke was applied to those with meningovascular syphilis for whom death was not attributable to meningovascular syphilis. For the majority of patients with meningovascular syphilis, we assumed that death would be attributable to meningovascular syphilis (see Table A-1). For those whose death was attributable to meningovascular syphilis, we applied one-fourth the number of years of long-term care shown in this table.

Appendix Table A-10: Resources required for those treated for general paresis

Item	**Resources required, all patients**
Office visit, new patient	3
Lumbar puncture and cerebrospinal fluid (CSF) analysis	1
X-ray	1
CT scan	1
Day of hospitalization	10
Aqueous crystalline penicillin G 18–24 million units	10
Blood draw	2
RPR (rapid plasma reagin) test	2
Number of years of long-term care needed, among those not dying from general paresis	8 (range: 3 to 11)

Following Schmid and Zaidi,[8], we approximated the number of years of long-term care required for patients with general paresis using the median survival time following a diagnosis of Alzheimer's disease. We applied a base case estimate of 8 (range: 3 to 11), based on the median value of 8.3 for those diagnosed at age 65 years in a survival study by Brookmeyer et al. (2002),[32] and we applied a range of 3 to 11 based on the most extreme values reported in that study (2.7 to 10.6) when stratified by age at diagnosis and sex. The number of years of long-term care shown in this table among those treated for general paresis who have stroke was applied to those with general paresis for whom death was not attributable to general paresis. For the majority of patients with general paresis, we assumed that death would be attributable to general paresis (see Table A-1). For those whose death was attributable to general paresis, we applied one-fourth the number of years of long-term care shown in this table.

Appendix Table A-11: Probabilities applied when estimating the costs of the decision tree outcomes listed in Table 2 of main manuscript

Outcome	Probability		
	Base case value	Lower value	Upper value
Probability that patients treated for syphilis receive recommended follow-up	0.373[33]	0.07[34]	0.809[35]
Among those treated for syphilis of unknown duration or latent syphilis, probability that lumbar puncture is performed	0.310[36]	0**	0.770[36]
Probability that those treated for neurosyphilis or ocular syphilis receive therapy option with higher cost (intravenous aqueous crystalline penicillin G)	0.213[37]	0.140***	0.293***
Probability of surgery among patients treated for cardiovascular syphilis	0.500[8]	0.250†	0.750†
Probability of stroke among patients treated for meningovascular syphilis	0.750[8]	0.500†	1†
Probability that stroke patients require long-term care	0.170[38]	0.070	0.390
Probability of death from cardiovascular, tabes dorsalis, meningovascular, or general paresis; given these conditions [see Appendix Table A-1]	0.730[6]	0.513	0.869

**Given limited data, a lower bound of 0 was applied.
***Approximated as 1st and 99th percentiles of binomial distribution, using base case estimate in which 32/150 patients were treated with intravenous aqueous penicillin G and 118/150 were treated with intramuscular aqueous procaine penicillin G with oral probenecid. As noted in text, a higher percentage of patients in some settings might receive IV therapy, such as 72% of patients with ocular syphilis in North Carolina.[39] However, the upper bound we applied (0.293) reflects the upper bound for the national average (not for a single state) and was intended to be conservative.
†These ranges were assumed and were calculated as the base case value plus or minus 0.25 to include a wide range of plausible values.

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