# Parameter List

|  |  |  |
| --- | --- | --- |
| Parameter | Value | *Reference* |
| Initial infection |  |  |
| Estimated prevalence of diagnosed/undiagnosed syphilis in 1940 | 0.007 (+/- 50%) | *(United States Census Bureau 1944, Centers for Disease Control and Prevention (CDC) 2024)* |
| Proportion of infections by stage | Primary= 0.45  Secondary= 0.13  Early latent = 0.29  Late latent = 0.4  Tertiary = 0.13 | *(Centers for Disease Control and Prevention (CDC) 2024)* |
| Sex ratio at birth |  |  |
| Ratio of male to female births | 1.048 [1.04 - 1.06] | *(Mathews and Hamilton 2005) (Expanding the lower bound to capture more uncertainty at the MSA level)* |
| Syphilis Natural History |  |  |
| Duration of primary syphilis | 2 - 6 weeks | *(Lafond and Lukehart 2006, Kent and Romanelli 2008, Gross and Tyring 2011, Hicks and Clement 2021, Mercuri, Moliterni et al. 2022)* |
| Duration of secondary syphilis | 1 - 3 months | (Singh and Romanowski 1999, Gross and Tyring 2011, Hicks and Clement 2021) |
| Relapse from Early Latent to Secondary Syphilis | 25% | (Singh and Romanowski 1999) we simplify to assume all relapses happen in the first year during early syphilis |
| Proportion of Early Symptomatic disease |  |  |
| Proportion of incident cases presenting with symptomatic primary syphilis among MSM | 20 - 29% | (Peel, Chow et al. 2021)  In absence of data for heterosexual male and female, the same value and ranges are used for all subgroups |
| Proportion of incident, non-primary cases presenting with symptomatic secondary syphilis among MSM | 15 - 17% | (Peel, Chow et al. 2021) |
| Progression Rates |  |  |
| Primary & Secondary to CNS | [0.036 – 0.091] | (Golden, Marra et al. 2003, Kent and Romanelli 2008, De Voux, Kidd et al. 2018) |
| Early latent to CNS | 0.012 | (De Voux, Kidd et al. 2018) |
| Late Latent to CNS | Male: 0.00454  Female: 0.00225 | From Table 9 and Fig 12, we extract the proportion of patients developing different types of neurosyphilis, and duration of time to diagnosis, by type and sex, and calculate the total rate by sex |
| Late latent to tertiary syphilis | Male: 0.01077  [0.00975 - 0.011794]  Female: 0.01035  [0.00850 - 0.012192] | Assuming the rates are independent, we can combine the means and variances of the two outcomes for late benign and cardiovascular syphilis. Since we don't have the standard deviation (SD) for cardiovascular events, we'll use the SD from benign late syphilis as a proxy.  To estimate the 95% confidence interval range, we use the normal approximation, calculating the half-width as 1.96×SD. |
| * Rate of developing Late Benign Syphilis | Male: 0.00558 [sd= 0.00052]  Female: 0.00751 [sd= 0.00094] | Table 7 reports cumulative percentage of cases developing benign late syphilis by the end of the 15th, 30th, and 35th years (Clark and Danbolt 1955). Using this data, we fit a linear model to the logit transformation of the cumulative proportions of individuals developing late benign syphilis by the 15th, 30th, and 35th years post-infection (assuming no intercept).The linear model is then used to estimate the average rate of change in the risk of developing the disease per year, as well as the standard deviation of this estimated rate |
| * Rate of developing cardiovascular syphilis (complicated and uncomplicated types) | Male: 0.005186745  Female: 0.002837651 | (Clark and Danbolt 1955)  Rates are computed from reported proportion of patients developing various sypes of cardiovascular syphilis and time to diagnosis (not the onset of symptoms) |
| Transmissions |  |  |
| Transmissibility from primary versus secondary syphilis | 1 | (Alexander and SCHOCH 1949) |
| Transmissibility from Early Latent versus primary/secondary syphilis | ? |  |
| Vertical Transmission & Congenital Syphilis |  |  |
| Probability of vertical transmission from mothers with early syphilis | 50% [30 - 60%] | (Ingraham Jr 1950, Fiumara, Fleming et al. 1952, Cooper and Sánchez 2018, Fang, Partridge et al. 2022) |
| Probability of vertical transmission from mothers with late syphilis | 10% [0.05 -15%] |  |
| Relative risk of vertical transmission among mothers with no prenatal screening (untreated syphilis) | 0.36 [0.28 - 0.449] | (Qin JiaBi, Yang TuBao et al. 2014) |
| Relative risk of vertical transmission among mothers receiving prenatal screening (syphilis treatment) | First trimester= 0.104 [0.077 - 0.14]  Second trimester= 0.176 [0.118 - 0.254]  Third trimester = 0.406 [0.313 - 0.507] | (Qin JiaBi, Yang TuBao et al. 2014) |
| Maternal treatment success in preventing congenital syphilis | 100% | (Alexander, Sheffield et al. 1999) |
| Proportion of multi-births (not singleton) | 3.1% | (March of Dimes 2023) |
| Syphilis treatment cascade |  |  |
| Proportion of diagnosed cases immediately treated (within 30 days) | 89% |  |
| Rate of delayed treatment | 1.91 per month |  |
| Contact tracing |  |  |
| Proportion of index cases interviewed (with Early syphilis) | 80% [30 - 98%] | (Brewer 2005, Katz, Hogben et al. 2010, Hoots, Lewis et al. 2014, Samoff, Cope et al. 2017, Cope, Bernstein et al. 2022, Kerani, Chang et al. 2024) |
| Partners receiving new diagnosis/treatment per index case | 0.1 [0.05, 0.2] |
| Partners receiving empiric treatment (who are truly infected) per index case | 0.1 [0.04, 0.19] |
| Proportion of diagnosed contacts in primary and secondary stage | 57%  (assuming 0.25%in primary and rest in secondary) | (Samoff, Cope et al. 2017) |
| Proportion of diagnosed contacts in early latent stage | 50% of not those in PS | Assumption |
| Mortality |  |  |
| Mortality from untreated tertiary syphilis |  |  |

* **Transmissibility data for the primary, secondary, and early latent stages of syphilis**. For now, we’re assuming similar infectiousness between the primary and secondary stages, but we are still looking into potential reductions in transmission during the early latent stage compared to primary and secondary stages.
  + **The likelihood of infectiousness in the latent stage is minimal and our assumption …**
* **Mortality for tertiary syphilis**
* **Proportion of Early Symptomatic Disease**: We've only found data for MSM and plan to use these estimates for heterosexual men as well. However, we are still missing similar estimates for women, particularly the proportion of incident cases presenting with symptomatic primary and/or syphilis

**Women with primary syphilis are 25-50% less symptomatic.**

# Estimating the size of initial infection in 1940

Due to the unavailability of syphilis prevalence data for 1940, we rely on the reported number of syphilis diagnoses from the CDC, which documented 485,560 cases (a rate of 368.2 per 100,000 persons) that year (Centers for Disease Control and Prevention (CDC) 2024). This total includes all stages of syphilis, congenital syphilis, and cases where the stage of syphilis was not specified.

To estimate the number of non-congenital syphilis cases, we first adjust for congenital syphilis by removing the proportion of reported cases identified as congenital. This adjustment reduces the total number of non-congenital diagnoses to 464,079 cases.

Next, we estimate the U.S. population size in 1940 using historical reports (United States Census Bureau 1944). After excluding the population under 5 years of age, the adjusted population size is 130,615,123 persons.

To account for missed diagnoses and individuals living with undiagnosed syphilis, we assume that only 50% of syphilis cases were reported during this time, based on historical estimates.

Using these assumptions, we estimate that approximately 0.7% of the U.S. population in 1940 was either diagnosed or living with undiagnosed syphilis.

It is important to note that this estimate is subject to significant uncertainty. The assumptions made—such as the reporting rate of 50%, the adjustment for congenital syphilis, and the exclusion of the population under 5 years—introduce variability. To account for these uncertainties, we assume a wide interval for the prior value of syphilis prevalence, allowing for a 50% variation (both high and low) around the estimated prevalence. This approach helps to incorporate the potential variability in the assumptions and reporting practices, providing a more flexible range for the true prevalence of syphilis in 1940.

**Proportion of prevalent cases by stage of infection:** In the next step, we rely on the reported proportions of syphilis diagnoses by stage to estimate the proportion of prevalent cases in each stage of infection. The reported data includes the total number of diagnoses in the following stages: combined primary and secondary stages, early latent, and those with late latent or unknown duration. We begin by calculating the proportion of total diagnoses in each stage based on the reported data.

To estimate the breakdown within the primary and secondary stages, we assume that 25% of the reported cases in the combined primary and secondary category are in the primary stage, based on the relative duration of this stage. The remaining cases are assumed to be in the secondary stage. For the cases reported as late latent or with unknown duration, we assume that 25% fall into the tertiary stage, and the remaining 75% are assigned to the late latent stage.

The estimate of syphilis prevalence by stage is subject to several sources of bias. First, the reliance on reported diagnoses by stage introduces potential inaccuracies when approximating prevalent cases. Symptomatic disease, particularly in the primary, secondary, and tertiary stages, is more likely to trigger case seeking and is easier to diagnose correctly. This may lead to an overrepresentation of the symptomatic stages in the estimates. Furthermore, our adjustments to reported estimates by stage introduce additional biases. The assumption that 25% of cases in the primary and secondary stages are primary, based on stage duration, may not accurately reflect the actual distribution of cases, leading to misclassification bias. Additionally, the method assumes that 25% of late latent or unknown duration cases are tertiary, which may not be representative of the actual progression of the disease, introducing further bias. Finally, the assumption of homogeneous stage durations and the generalization of the disease’s progression across all demographic groups may not reflect population-specific variations, leading to potential selection bias. These biases collectively introduce uncertainty in the estimate. However, given the limited role of this parameter in estimating the burden of infection in 1940, we believe that potential biases may have a minimal impact on the overall results. This is because the Bayesian calibration process will fit the simulations to historical trends in syphilis diagnoses over time, effectively adjusting for biases in regional infection sizes. As long as these biases do not distort the overall trajectory of the epidemic, the majority of individuals with prevalent disease from that time frame would not survive to the present day, and therefore would not influence the experimental scenarios. Consequently, while these biases may introduce some uncertainty, they are unlikely to significantly affect the key findings of the analysis.

# Natural History of Syphilis

Syphilis is a multistage disease with diverse and wide-ranging clinical manifestations that vary depending on the stage of infection, which often includes overlapping phases. In our compartmental model, we represent the natural history of syphilis through XX distinct stages. These stages are defined based on clinical symptoms (which trigger care-seeking), infectiousness (the potential for transmission), and the associated risks of mortality and disability (which influence the burden of disease and costs).

>Khalil: For simplicity, we classify syphilis into two broad periods: early infection (within the first year after transmission) and late infection (beyond one year). Early infection is sexually infectious, while late infection is not. Vertical transmission from mother to unborn child is assumed to occur throughout the entire course of untreated disease, with the majority (approximately 75%) of such transmissions occurring during the early stage of infection.

## Primary syphilis:

Within the early infection period, we assume that **primary syphilis** is characterized by the development of a painless chancre (sore), which represents an initial local infection. The chancre typically resolves spontaneously without treatment, but the disease quickly becomes systemic as *T. pallidum* disseminates throughout the body. Individuals in the primary stage are sexually infectious, and care-seeking behavior varies. In heterosexual men, primary chancres most commonly occur on the penis, while 32-36% of homosexual men have chancres in less visible locations, including the rectum, anal canal, and oral cavity. For women, primary chancres are usually found on the labia or cervix. Due to the painless nature of the chancre and its potential location in inconspicuous sites, syphilis diagnosis in women and homosexual men is often delayed until later disease manifestations become evident. Reported duration of primary syphilis (Duration of chancre): 3-6 weeks *(Kent and Romanelli 2008, Mercuri, Moliterni et al. 2022),*  2-6 weeks (Lafond and Lukehart 2006, Hicks and Clement 2021), 4-6weeks(Gross and Tyring 2011)

* *Primary incubation****:*** *Primary syphilis occurs 21 days (3 to 90) days after exposure when the first chancre develops (Kent and Romanelli 2008, Mercuri, Moliterni et al. 2022)- excluded from our model*
* *Secondary incubation: The treponemes proliferate in the chancre and are carried via lymphatics to the bloodstream, from which they disseminate throughout the body. The time at which the secondary lesions make their appearance basically depends on two factors: the virulence of the treponeme and the systemic response of the host. Secondary syphilis appears around 3 to 12 weeks from the disappearance of the chancre(Mercuri, Moliterni et al. 2022) – excluded from our model*

**Duration of primary syphilis (Duration of chancre): à 2-6 weeks *(Lafond and Lukehart 2006, Kent and Romanelli 2008, Gross and Tyring 2011, Hicks and Clement 2021, Mercuri, Moliterni et al. 2022)***

## Secondary syphilis

We assume that **secondary syphilis** is characterized by systemic symptoms, with the most prominent clinical sign being a rash that can present in various forms. Similar to primary syphilis, the symptoms of secondary syphilis typically resolve spontaneously even without treatment. This stage is highly infectious, and we estimate that 70-80% of individuals with secondary syphilis experience symptoms, with a subset of them seeking care. Delay to heal in absence of treatment: 1-2months (Hicks and Clement 2021), within 3 months (Gross and Tyring 2011), *2–12 wk (2 wk–6 mos) (Singh and Romanowski 1999)*

* **Duration of secondary syphilis: 1-3 months (Singh and Romanowski 1999, Gross and Tyring 2011, Hicks and Clement 2021)**

## Relapse EL to Secondary

## Early Latent

The latent phase begins when symptoms resolve but the individual remains infected, as confirmed by serologic testing. We assume that **early latent** syphilis refers to infections acquired within the past 12 months. Individuals in this stage remain sexually infectious, although less so than those in primary or secondary syphilis. Approximately 25% of individuals in the early latent phase may **relapse** to secondary syphilis, temporarily increasing their infectiousness and likelihood of seeking care. *About 90% of first relapses occur within 1 year, 94% occur within 2 years, and the rest occur over 4 years. (Singh and Romanowski 1999)*

* **Proportion relapse : 25% (Singh and Romanowski 1999) and we simplify to assume all relapses happen in the first year (EL)**

## Proportion of primary/secondary symptomatic disease

“We are now [assuming] that only a percentage of cases in the primary/secondary stage are symptomatic, and among those with symptoms, some percentage of cases don’t recognize symptoms.”

**Parameter:** Proportion of primary/secondary symptomatic disease among MSM (also applied to heterosexual men)

**Summary:**

* MSM attending 3-monthly visits at a PrEP clinic in Melbourne, Australia between Feb 2016 – Mar 2019
* Underwent routine STI screening with serological testing for syphilis at visits but could also attend walk-in clinic outside of their visits
* Syphilis diagnoses classified using Australian laboratory case definition (seroconversion with prior negative serology within 24 months or a 4-fold rise in RPR if reinfection); classified as primary/secondary based on clinical exam and lab results (PCR from a lesion and/or serology)
* Results (Table 1) : (Peel, Chow et al. 2021)
  + Total of 69 incident syphilis cases (24 primary, 16 secondary, 29 early latent)
  + Among all 69 cases, 20 presented reporting symptoms of primary syphilis, 14 of whom were diagnosed at walk-in STI clinic *between* PrEP appointments
    - 🡪 **Proportion of incident cases presenting with symptomatic primary syphilis = 20-29%** (14/69 – 20/69) (Peel, Chow et al. 2021)
  + Among the cases who were *not* primary (45 cases), 8 presented reporting symptoms of secondary syphilis, 7 of whom were diagnosed at walk-in STI clinic *between* PrEP appointments
    - 🡪 **Proportion of incident, non-primary cases presenting with symptomatic secondary syphilis = 15-17%** (7/45 – 8/45) (Peel, Chow et al. 2021)

**Parameter:** Ratio of primary/secondary symptomatic disease among women relative to MSM

* **Summary:**   
  Berzkalns, et al (2023) analyzed surveillance data from King County between 2007 and 2022 to examine incidence trends of syphilis, stratified by stage and gender(Kerani, Chang et al. 2024). Among women, the majority of syphilis cases (76%) each year were classified as late or of unknown duration, with the percentage ranging from 58% to 96%. However, by 2020, the rate of early syphilis in women surpassed that of latent or unknown duration syphilis. By 2022, 52% of all syphilis cases in women were classified as early.
* From 2007 to 2010, 5% of cisgender women with late or unknown duration syphilis had an RPR titer ≥1:32. This increased to 26% from 2011 to 2020, and 54% in 2021 to 2022, indicating a rise in recent infections.
* Assuming that these recent infections were missed due to the lack of symptoms, we estimated the total number of early infections (including both early stage diagnoses and late/unknown stage cases with high RPR titers) and calculated the proportion that were symptomatic. We applied a similar method to estimate this proportion for MSM (men who have sex with men) in this study.
* Finally, we compared the ratio of symptomatic early syphilis cases in women to those in MSM.
* This results in a ration of 95%, 62%, 42% from 2007-2010, 2011-2020, and 2021-2022 respectively. The weighted mean value over 2007-2022 is 67%. Given that women have a lower probability of symptomatic disease in the primary stage compared to the secondary stage, we apply this ratio only to infections in the primary stage. For infections in the secondary stage, we assume that women have a similar symptomatic ratio to MSM.
  + - **Ratio of symptomatic disease in the primary stage among women relative to MSM= 67%**

## Late Disease

**Late latent** syphilis is assumed to occur when the infection has persisted for more than 12 months. We assume that individuals with late latent syphilis are not sexually infectious, as they lack the lesions necessary to transmit the disease to sexual partners. Late in the latent stage of syphilis, clinical manifestations are lacking, but serological tests are still positive; however, the intensity of serological reactions decreases gradually. The pathogen may occasionally persist in the bloodstream, although in small numbers, and can cause vertical infection (transmission from the mother to the fetus), but this occurs only infrequently. At this stage, the infection is no longer communicable by sexual intercourse.

**Neurosyphilis:** We include a distinct stage in the model to represent central nervous system (CNS) involvement, known as neurosyphilis, which can occur at various points during disease progression. Neurosyphilis manifests in several clinical forms depending on the timing and affected area. For modeling purposes, we focus on symptomatic CNS involvement due to its significant impact on care-seeking behavior.

Early symptomatic neurosyphilis, such as meningeal neurosyphilis, typically occurs within the first year of infection and presents with symptoms like headaches, neck stiffness, nausea, photophobia, and cranial nerve involvement. Late symptomatic neurosyphilis forms include meningovascular neurosyphilis, which generally arises 5–12 years post-infection and is associated with ischemic strokes caused by inflammation of cerebral blood vessels. Additional late-stage forms include *tabes dorsalis*, characterized by severe pain, sensory ataxia, loss of proprioception, and Argyll Robertson pupils, as well as *general paresis*, which involves progressive cognitive decline, personality changes, psychosis, and motor deficits. Furthermore, ocular and otic neurosyphilis may lead to uveitis, optic neuropathy, hearing loss, tinnitus, or vertigo, potentially resulting in permanent disability if untreated.

**Tertiary:** Tertiary syphilis describes patients with late syphilis who have **symptomatic** manifestations involving the cardiovascular system or gummatous disease (granulomatous disease of the skin and subcutaneous tissues, bones, or viscera) or neurologic involvement. Appearance of these presentations is dependent on where T.Palldium dissemination occurs within the body.

Cardiovascular syphilis typically presents with complications such as aortic aneurysms, aortic regurgitation, and coronary artery ostial stenosis. Gummatous syphilis is characterized by granulomatous, nodular lesions, which, although rare, can occur in various organs, most commonly the skin and bones. These lesions are generally benign unless their destructive effects involve vital organs, a condition often referred to as "late benign syphilis." (Gross and Tyring 2011) Late neurological manifestations of syphilis can also arise, including forms like tabes dorsalis and general paresis.

### CNS

#### Rate of developing neurosyphilis from early stages

**Summary:** Among cases reported in 2015 in 10 states, provided percentage with either confirmed or probable neurosyphilis by stage **(De Voux, Kidd et al. 2018)**

* + Primary: 0.3%
  + Secondary: 1.1%
  + Early latent: 0.8%
* Using the formula of rate = (-ln(1-prob))/time, we get the following rates:
  + Primary
    - Assuming time = 1 month
    - rate: (-ln(1-.003))/(1/12) =
      * **primary 🡪 0.03605411**
  + Secondary
    - Assuming time = 3 months
    - rate: (-ln(1-.011))/(3/12)
      * **secondary 🡪 0.04424379**
  + Early latent
    - Assuming time = 8 months
    - rate: (-ln(1-.008))/(8/12)
      * **early latent 🡪 0.01204826**

**Golden (2003) & Kent (2008)** estimate that 25–60% of patients experience CNS invasion during the primary and secondary stages, with 5% of these cases being symptomatic. Proportion of patients developing symptomatic CNS during the primary and secondary stages = 5%\* [25-60%]=[1.25–3%] (Golden, Marra et al. 2003, Kent and Romanelli 2008)

* + - **PS.to.CNS rate LB = (-ln(1-.0125))/(4/12)=0.037**
    - **PS.to.CNS rate UB= (-ln(1-.03))/(4/12)=0.091**

**Final Estimates:**

* **Primary/secondary to CNS: [0.036 – 0.091](Golden, Marra et al. 2003, Kent and Romanelli 2008, De Voux, Kidd et al. 2018)**
* **Early latent: 0.012 (De Voux, Kidd et al. 2018)**

#### Rate of developing neurosyphilis from late stage

We use data from the Oslo study: Following 2,000 untreated patients with primary and secondary syphilis during the twenty-year period, 1891–1910 (Clark and Danbolt 1955). Table 9 shows the proportion of cases developing neurosyphilis by type and sex, Fig 12 shows duration of infection at discovery, in years, by type and sex

A table of numbers and text

AI-generated content may be incorrect.A graph of a number of men and women

AI-generated content may be incorrect.

From Table 9 and Fig 12, we extract the proportion of patients developing neurosyphilis, and duration of time to diagnosis, by type and sex, and the

|  |  |  |  |
| --- | --- | --- | --- |
|  | Proportion | Time to diagnosis | Rate |
| diffuse.meningovascular | 3.6% | 14.9 | 0.0024606701 |
| general.paresis | 3.0% | 25.4 | 0.0011991814 |
| tabes.dorsalis | 2.5% | 28.8 | 0.0008790906 |
| gumma.of.brain | 0.3% | NA | NA |
| Male Total |  |  | **0.004538942** |
| diffuse.meningovascular | 1.7% | 18.8 | 0.0009120297 |
| general.paresis | 1.7% | 19.6 | 0.0008748040 |
| tabes.dorsalis | 1.4% | 30.7 | 0.0004592484 |
| gumma.of.brain | 0.2% | NA |  |
| Female Total |  |  | **0.002246082** |

### Tertiary syphilis

We use data from Oslo study, following 2,000 untreated patients with primary and secondary syphilis during the twenty-year period, 1891–1910 (Clark and Danbolt 1955). We first compute the rate of developing late benign and cardiovascular syphilis, and then add them to compute total tertiary rate in the model.

#### Late Benign

**Late benign syphilis:** cumulative percent developing benign late syphilis by the end of the 15th, 30th, and 35th years

A close-up of a chart

AI-generated content may be incorrect.

Table 7 reports cumulative percentage of cases developing benign late syphilis by the end of the 15th, 30th, and 35th years (Clark and Danbolt 1955). Using this data, we fit a linear model to the logit transformation of the cumulative proportions of individuals developing late benign syphilis by the 15th, 30th, and 35th years post-infection (assuming no intercept).The linear model is then used to estimate the average rate of change in the risk of developing the disease per year, as well as the standard deviation of this estimated rate

* rate.male.benign.late.est: 0.00558 [sd= 0.00052]
* rate.female.benign.late.est: 0.00751[sd= 0.00094]

#### Cardiovascular Syphilis

from Fig9: Percentages of each agegroup and all ages of the “known” 953 cases who developed some type of cardiovascular involvement

A graph of age-related diseases

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**Table 8** shows the proportion of cases developing different types of cardiovascular syphilis by age . **Figure 10** shows the duration of infection at the time of diagnosis of cardiovascular syphilis (not the onset of symptoms).

A table of blood vessels

AI-generated content may be incorrect.A graph of different types of syphilis

AI-generated content may be incorrect.

From Table 8, we estimate the total proportion developing uncomplicated and complicated cardiovascular syphilis for men and women, and estimate the duration of infection at diagnosis from Figure 10. Note that this is not the duration to onset of sypmpthoms.

Assuming that the rate of event is fix over time, the time to event is distributed exponentially and we can use Rate: -ln(1-p)/t to compute the rate of event from the cumulative proportion experiencing the event (P) by time t.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Proportion | Time to diagnosis | Rate |
| Male: uncomplicated aortitis | 0.026 | 28.9 | 0.0009115562 |
| Male: Total complicated | 0.123 | 30.7 | 0.0042751885 |
| Male Total |  |  | 0.005186745 |
| Female: uncomplicated aortitis | 0.029 | 23.7 | 0.001241722 |
| Female: Total complicated | 0.051 | 32.8 | 0.001595929 |
| Female Total |  |  | 0.002837651 |

#### Estimating final Tertiary syphilis rates:

Assuming the rates are independent, we can combine the means and variances of the two outcomes for late benign and cardiovascular syphilis. Since we don't have the standard deviation (SD) for cardiovascular events, we'll use the SD from benign late syphilis as a proxy. To estimate the 95% confidence interval range, we use the normal approximation, calculating the half-width as 1.96×SD.

* rate.male.tertiary.late.range= 0.010771530 [0.009749247 0.011793814]
* rate.female.tertiary.late.range= 0.010346077 [0.008499934 0.01219222]

# Infectiousness

Some studies suggest that the infectiousness of syphilis varies across its stages, influenced by clinical manifestations and the presence of lesions that facilitate transmission. During primary syphilis, infectiousness is high due to chancres, which are filled with *Treponema pallidum*. The risk remains elevated in secondary syphilis, characterized by mucocutaneous rashes and condylomata lata, both rich in bacteria and highly transmissible. However, despite these suggestions in the literature, we could not find a study directly linking a relative increase in infectiousness across stages.

A study by Alexander & Schoch (1949), which treated individuals known to have been in contact with patients infected with syphilis, included those with recent exposure to primary or secondary syphilis. Of the 51 individuals exposed to primary syphilis, 62.7% became infected, while 61.8% of the 110 exposed to secondary syphilis were infected. This suggests that transmissibility from primary syphilis is similar to that of secondary syphilis (Alexander and SCHOCH 1949). In the absence of definitive estimates, we assume similar transmissibility for primary and secondary syphilis.

Early latent syphilis retains moderate infectious potential due to occasional relapses of secondary symptoms. In contrast, late latent syphilis and tertiary syphilis are considered non-infectious, as they lack active lesions. However, congenital syphilis transmission depends largely on the maternal stage of infection, with the highest risk occurring during early syphilis (within 12 months of infection), when bacterial loads are at their peak (see below)

# Vertical transmission and congenital syphilis

## Proportion of multibirths

In the United States in 2023, 96.9% of all live births were singleton births and 3.1% were multiple births.(March of Dimes 2023)

Race specific estimates if we need them later on: In the United States during 2021-2023 (average), the multiple birth ratio (per 1,000 live births) was highest for Black infants (42.1), followed by Whites (33.1), American Indian/Alaska Natives (27.3), Hispanics (24.9) and Asian/Pacific Islanders (24.3).

## Probability of vertical transmission:

Vertical transmission is related to the stage of maternal syphilis, with the highest transmission rates seen with early syphilis and specifically, secondary syphilis.

* In 1950, Ingraham reported that among 251 women with untreated syphilis of less than 4 years’ duration, 41% of their infants were born alive and had congenital syphilis, 25% were stillborn, 14% died in the neonatal period, 21% had low birth weight but no evidence of syphilis, and only 18% were normal full term infants. Among mothers with late latent infection, only **2% of their infants had congenital syphilis** (Ingraham Jr 1950)
* In 1952, Fiumara and colleagues reported that untreated maternal primary or secondary syphilis resulted in 50% of infants having congenital syphilis while the other 50% were stillborn, premature, or died in the neonatal period. With early and late latent infection, **40% and 10%** of infants, respectively, had congenital syphilis. (Fiumara, Fleming et al. 1952)
* More recently, from 1988 to 1998 at Parkland Memorial Hospital, Dallas, Sheffield and colleagues reported vertical transmission rates of **29%, 59%, 50%,** and **13% in** mothers with primary, secondary, early latent, and late latent infection, respectively.(Sheffield, Sanchez et al. 2002)

Using these studies, we characterize the probability of vertical transmission in the early (<=12months post infection) versus late stage (>12 months post infection) as follow:

* Probability of vertical transmission from mothers with early syphilis: 50% [30 - 60%]
* Probability of vertical transmission from mothers with late syphilis: 10% [0.05 -15%]

## RR congenital syphilis based on Prenatal care:

The most comprehensive study we found is a Systematic Review and Meta-Analysis of the Literature by Qin et al. (2014). The authors report the proportion (%) of adverse pregnancy outcomes (APOs) among women with syphilis and women without syphilis (Table 2). In a subgroup analysis, they further report the proportion of APOs among syphilis-infected women based on the timing of syphilis treatment during pregnancy (first, second, or third trimester) (Table 6). We rely on the pooled incidence rates reported in the study, along with their corresponding 95% confidence intervals. The combined incidence and confidence intervals were calculated using fixed-effects models, or, in the presence of heterogeneity, random-effects models.

\*\* Of note, the reported proportion of births resulting in congenital syphilis among untreated mothers is 36%, which is slightly lower than the proportion among mothers receiving treatment in the third pregnancy trimester (40.6%). While this may seem counterintuitive, several factors could explain this. Treatment in earlier pregnancy stages is generally more effective, and women receiving third-trimester treatment may have been diagnosed later, after the infection had already progressed. This delay in treatment could increase the risk of transmission. Additionally, untreated women may have syphilis at varying stages, with not all cases resulting in congenital syphilis. Late-stage syphilis or other factors could contribute to the difference. Reporting or data biases might also influence the observed proportions.

**Risk of congenital syphilis**  (Qin JiaBi, Yang TuBao et al. 2014)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Congenital | M (IQR) of reported proportions in the original studies | | | summary state (95% CI) calculated using fix effects or random effects models | | |
| untreated | 34.4 | 23.7 | 68.3 | 36% | 28 | 44.9 |
| treated women with syphilis | 13.9 | 8.2 | 21.9 | 14% | 10.5 | 18.5 |
| first | 8.2 | 5.4 | 9.4 | 10.4% | 7.7 | 14 |
| second | 19.1 | 8.7 | 27.8 | 17.6% | 11.8 | 25.4 |
| third | 45 | 26.5 | 60 | 40.6% | 31.3 | 50.7 |

These estimates align with reported efficiency of syphilis treatment by Hawkes, et al. (2013): The odds of congenital syphilis among infants born to mother receiving intervention (to include screening and treatment) in the third trimester compared to first and second trimesters: **odds ratio 2.92,** 95% CI [0.66, 12.87].The overall odds ratio for any adverse outcome was 2.24 (95% CI 1.28, 3.93). (Hawkes, Gomez et al. 2013)

### Adequate treatment

* Six jurisdictions that participated in SET-NET conducted enhanced surveillance among people with syphilis during pregnancy based on case investigations, medical records, and linkage of laboratory data with vital records (Tannis, Miele et al. 2022)
* Inadequate treatment identified as: 1) treatment other than benzathine penicillin G, 2) treatment initiated less than 30 days before pregnancy outcome, 3) receipt of fewer than three doses (for late latent or unknown syphilis only), and 4) doses outside of the recommended dosing interval
* Results:
  + *As of September 15, 2023, of 1,476 people with syphilis during pregnancy, 855 (57.9%) were adequately treated and 621 (42.1%) were inadequately treated or not treated.*
  + *Among pregnant people who received timely prenatal care (n=1,143),* ***32.1% did not receive adequate treatment****, 17.3% received inadequate treatment, and 14.8% did not receive treatment during pregnancy.*
  + *The most common reasons for inadequate treatment among those with timely prenatal care were treatment initiation less than 30 days before pregnancy outcome (57.0%, despite receiving timely prenatal care), receiving fewer than three doses for those diagnosed with late latent or unknown syphilis (39.4%), and receiving doses more than 9 days apart (31.3%; data not shown)*

### Success of therapy:

* Additionally, maternal treatment of perinatal syphilis with penicillin (single IM dose for primary/secondary/early latent syphilis and three weekly doses for latent/tertiary syphilis) is considered adequate if the mother initiates (i.e., receives one dose) treatment at least 30 days before delivery (Workowski 2021).
* The success of therapy in preventing congenital syphilis was as follows: primary syphilis, 27 of 27; secondary syphilis, 71 of 75; early latent syphilis, 100 of 102; and late latent syphilis, 136 of 136. The success rate for all stages of syphilis was 334 of 340 (98.2%). (Alexander, Sheffield et al. 1999)

# Treatment cascade

## Proportion immediately treated following diagnosis

**Reference (1):** Robinson CL, Young L, Bisgard K, Mickey T, Taylor MM. Syphilis time to treatment at publicly funded sexually transmitted disease clinics versus non–sexually transmitted disease clinics—Maricopa and Pima Counties, Arizona, 2009–2012. Sexually transmitted diseases. 2016 Jan 1;43(1):30-3. (Robinson, Young et al. 2016)

**Summary:**

* Primary and secondary syphilis cases reported from during the period January 1, 2009, to December 31, 2012 were obtained from Arizona's STD surveillance system
* Reports time to treatment among syphilis cases reported in Maricopa and Pima counties from 2009-12
* “Among all patients, 592 (67%) were treated 7 days or less after evaluation; 711 (80%) were treated 14 days or less after evaluation; 764 (86%) were treated 21 days or less after evaluation; 786 (89%) were treated 30 days or less after evaluation; 809 (92%) patients were treated 90 days or less after evaluation; 3 (<1%) were treated more than 90 days after evaluation; and 72 (8%) had no reported treatment.”

1- we define immediate treatment among those receiving treatment in less than a month

**proportion.immediately.treated= 0.89**

2- rate of delayed treatment : # p = 1-e(-rt)

#among remaining proportion (1-0.89=11%) not treated within a month, what proportion were treated within 60days:

p= (.92-.89)/(1-0.89)= 0.27 t = 2/12 #2 months

**r= -log(1-p)/t -> r= 1.91 #rate of delayed treatment**

**Reference (2):** Chen SY, Johnson M, Sunenshine R, England B, Komatsu K, Taylor M. Missed and delayed syphilis treatment and partner elicitation: a comparison between STD clinic and non-STD clinic patients. Sexually transmitted diseases. 2009 Jul 1;36(7):445-51.

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6785738/>

**Summary:**

* Reports time to treatment among syphilis cases reported in Maricopa county from 2006-7; disaggregated by stage and STD clinic vs non-STD clinic

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Delays to treatment** | **Primary** | **Secondary** | **EL** | **Unknown** | **LL** |
| 0 | 111 | 111 | 111 | 111 | 111 |
| 1–7 | 36 | 62 | 52 | 82 | 46 |
| 8–14 | 7 | 34 | 26 | 68 | 52 |
| 15–30 | 39 | 13 | 29 | 14 | 26 |
| >30 | 7 | 5 | 19 | 5 | 40 |
| % >30 days | 0.035 | 0.022 | 0.08 | 0.018 | 0.145 |

Using this data, we estimate the proportion receiving immediate treatment for patients in the early stage at 95% and for those in late and unknown stage at 92% which is very close. We conclude that the distinction by stage is too small to include in the model

A table of diseased symptom

Description automatically generated

# Contact tracing

Contact tracing for syphilis, like other sexually transmitted infections (STIs), is typically carried out by public health agencies at the local, state, or national levels. This process involves identifying individuals who may have been exposed to syphilis and notifying them so they can be tested and treated as needed. While statistics from syphilis contact tracing are generally reported to the CDC, this data is not readily available online.

In the absence of a centralized data repository, we turned to the literature to identify studies that report on partner tracing efforts for syphilis infections in the United States. We used the findings from these studies to estimate the contact tracing cascade. Although the cascade involves several steps, we simplify it into three key parameters that can be used to estimate its impact on diagnosis and treatment:

* **Proportion of Index Cases Reached and Interviewed**
* **Number of Partners Newly Diagnosed and Treated per Index Case**
* **Number of Partners Receiving Correct Empirical Treatment per Index Case**

The first two metrics are directly extracted from each study. To estimate proportion of partners infected with syphilis among those receiving empirical treatment (but not tested for syphilis), we relied on reported syphilis prevalence among contacts who were tested, and applied that to the contacts receiving empirical treatment. Estimated values and ranges are presented in Table1.

# Miscellaneous

## Misclassification of syphilis stages

The definition of early latent infection requires within the past year, documented: laboratory evidence of seroconversion, fourfold titer increase, symptoms, or contact with an independently documented early syphilis case.. <https://journals.lww.com/stdjournal/fulltext/2005/03000/A_Randomized,_Comparative_Pilot_Study_of.2.aspx>

* This is misinterpreted to include patients with risky behavior, young age, or high nontreponemal test titers.
* Information on partners is increasingly difficult to obtain. most latent infections of less than 1 year’s duration would be erroneously classified as late latent due to the lack of evidence. <https://journals.lww.com/stdjournal/fulltext/2005/03000/A_Randomized,_Comparative_Pilot_Study_of.2.aspx>

**After review and comparison with CDC criteria, 32% of EL diagnosis were reclassified as LL, and 14% as Unknown,**

***>>> We can include this as measurement error - And it’s correlated between EL and LL***

Contact tracing:

the number of partners contacted and treated for newly identified syphilis fell from 0.55 per case in 196128 to 0.19 in 199129

Secondary: max =1

Primary Relative to secondary:

EL relative to secondary:

Diagnosis

We assume that there are two separate mechanisms for diagnosis:

**Screening**: This is based on underlying rates of STI screening among populations.

**Symptomatic Screening Rates**: These rates vary by syphilis stage—primary, secondary, tertiary, and CNS involvement.

For **primary syphilis**, the differential is higher among heterosexual men compared to MSM (men who have sex with men) and women.

**Secondary syphilis** has a higher symptomatic screening rate compared to primary syphilis.

The rates for **tertiary syphilis** and **CNS involvement** are the highest among all stages.

## Other studies on Tertiary syphilis:

Historical data provides insights into the progression of late syphilis.

* The Oslo Study, a prospective natural history study conducted from 1891 to 1951, followed 1,978 patients with primary or secondary syphilis. It reported a mortality rate of 17% for males and 8% for females, with **28%** of patients eventually developing clinically evident complications of late disease. These complications included **cardiovascular syphilis (10%),** **symptomatic neurosyphilis (65%),** and **late benign syphilis (16%).** Cardiovascular syphilis and neurosyphilis were observed more frequently in males, and autopsy findings often revealed evidence of cardiovascular involvement.
* Paul Rosahn's review of autopsy findings at Yale University (1917–1941) showed that 9.7% of individuals over 20 years old had clinical, laboratory, or autopsy evidence of syphilis, with about half untreated. Among syphilitic patients, 51% had specific late syphilitic lesions at autopsy, with **30%** of clinically diagnosed cases showing such lesions. Among 77 untreated cases with late syphilitic lesions, **83% were cardiovascular**, **7.6% neurological**, and **8.5% gummatous**. These manifestations generally appeared 15–30 years after the initial infection, often involving multiple overlapping symptoms.
* **Oslo Study (cited in Kent2008):** Eventually, 28% of patients developed clinically evident complications of late disease including cardiovascular syphilis (10%), symptomatic neurosyphilis(65%), or late benign syphilis (16%), with both cardiovascular and neurosyphilis occurring more commonly in males
  + If I multiple these proportions into 28% to approximate total proportions:  2.8% of patients developing cardiovascular syphilis, 4.5% developing late benign syphilis, and 18.2% developing symptomatic neurosyphilis
* **Boeck study (cited in Singh1999)** estimates that approximately 30% of the patients developed tertiary manifestations. Late benign syphilis was the most frequent manifestation, occurring in 14% of males and 17% of females, 1 to 46 years after healing of the secondary lesions. The incidence of clinically apparent cardiovascular syphilis was 13.6% in males and 7.6% in females, but the true incidence may have been higher had more autopsies been carried out. Symptomatic neurosyphilis developed in approximately 9.4% of males and 5.0% of females.
  + It’s unclear to me if the final proportions are after factoring in the 30% or not. I assume that they are.  However, these proportions are in contrast to Oslo’s study finding the majority of Tertiary cases as symptomatic neurosyphilis
* **Lanford (2006)** estimates the following proportions from the literature: Progressive inflammation caused gumma (late benign syphilis) in 15% of patients with untreated syphilis. Cardiovascular syphilis was observed in 10% of untreated patients. Symptomatic late neurosyphilis was recognized in 6.5% of untreated patients.
  + These results are inline with Boeck study
* **Golden (2003)** provides an estimate for the two forms of tertiary syphilis, at 2-5% over 20-30 years developing General Paresis, and 2-9% over 3-50 years developing Tabes Dorsalis, but it’s progressed among those with early CNS (25-60%)
  + This is approximately, 4-14% of those patients with early CNS>> 2-5% of all patients?

**Progression from LL to tertiary:**

* Late benign syphilis: 14% of males and 17% of females, 1 to 46 years post infection (Kent-2008, Golden-2003)
  + Everyone was followed until the event occurs, which means that the follow up time was unequal
  + Since we don’t know the distribution of followup time, we take an average: t = (1+46)/2=28.5
  + Rate = - log(1-prob)/time ->
    - -log(1- 14%)/28.5 = 0.53% men and -log(1- 17%)/28.5 =0.65% women
* Cardiovascular syphilis: 13.6% in males and 7.6% in females 10-30 years post infection (Kent-2008)
  + Rate = -log(1-0.136)/20 = 0.73% men and -log(1-0.076)/30 = 0.39% women

>> total rates added for each sex: 1.26% men / 1.04% women

**Progression from LL to CNS:**

* Symptomatic neurosyphilis:  9.4% of males and 5.0% of females over 4-25 years post infection (Kent-2008)
  + -log(1- 0.094)/14.5= 0.68% for men & -log(1- 0.05)/14.5= 0.35% for women

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