<https://journals.lww.com/stdjournal/fulltext/1996/01000/syphilis_control__the_historic_context_and.13.aspx>

# 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 *(1, 2),*  2-6 weeks (3, 4), 4-6weeks(5)

* *Primary incubation****:*** *Primary syphilis occurs 21 days (3 to 90) days after exposure when the first chancre develops (1, 2)- 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(1) – excluded from our model*

**Duration of primary syphilis (Duration of chancre): à 2-6 weeks *(1-5)***

### 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, Het men and Women

**Reference (MSM):** Peel J, Chow EP, Denham I, Schmidt T, Buchanan A, Fairley CK, Williamson DA, Bissessor M, Chen MY. Clinical presentation of incident syphilis among men who have sex with men taking HIV pre-exposure prophylaxis in Melbourne, Australia. Clinical Infectious Diseases. 2021 Aug 15;73(4):e934-7.

<https://academic.oup.com/cid/article/73/4/e934/6125283>

**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)
  + 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)
  + 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)

## 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 (3), within 3 months (5), *2–12 wk (2 wk–6 mos) (6)*

* **Duration of secondary syphilis: 1-3 months (3, 5, 6)**

## 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. (6)*

* **Proportion relapse : 25% (6) and we simplify to assume all relapses happen in the first year (EL)**

## 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." (5) Late neurological manifestations of syphilis can also arise, including forms like tabes dorsalis and general paresis.

### Probability of Developing Early CNS

**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 early stages = 5%\* [25-60%]=[1.25–3%] (2, 7)**

### Probability of Developing Late Neurosyphilis & Tertiary Disease

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?

**Final estimates: 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

### Using Probability to Inform Rates:

To estimate the rate of progression from each stage of syphilis, we calculate the proportion of patients experiencing specific outcomes over a given timeline. This is achieved using the following formula:

Exponential rate (λ)=−ln(1−probability)/time span

Here:

* **Probability** refers to the likelihood of progression to a specific stage or clinical manifestation of syphilis (e.g., CNS involvement or tertiary syphilis).
* **Time span** represents the period over which the progression occurs (e.g., from early to late stages of syphilis).

*This method assumes a constant hazard rate, which may need adjustment if incidence varies over time.*

# Infectiousness

The infectiousness levels of syphilis vary across its stages, driven by clinical manifestations and the presence of lesions that facilitate transmission. During primary syphilis, infectiousness is high due to chancres, which are teeming with *Treponema pallidum*. This risk peaks in secondary syphilis, characterized by mucocutaneous rashes and condylomata lata, both rich in bacteria and highly transmissible. Early latent syphilis retains moderate infectious potential, with occasional relapses of secondary symptoms. In contrast, late latent syphilis and tertiary syphilis are considered non-infectious due to the absence of active lesions. Congenital syphilis transmission, however, depends heavily on the maternal stage of infection, with the highest risk during early syphilis (within 12 months of infection) when bacterial loads are at their peak.

Secondary syphilis case patients also have infectious lesions (mucous patches and *condyloma lata*) which are present in approximately 30% of secondary case(8, 9)

Oxman Modeling: Primary 30%, secondary 75%

# Probability of vertical transmission:

* Stage of maternal syphilis
  + Primary/Secondary = 60-100%, EL: 40% LL: <8% [REF]
  + Among infants born to mothers with PS untreated disease, 50% had congenital and 50% had other adverse outcomes (stillborn premature, or died post birth). Among those born to mothers with EL and LL, 40% and 10% had congenital syphilis. [REF]
  + Primary, secondary, EL, LL transmission rate of 29%, 59%, 50%, 13% respectively [REF]
* Increase with gestational age

The risk to the fetus of congenital infection is 50 to 70% in pregnancies complicated by early syphilis but decreases to 15% if maternal syphilis was contracted more than a year before the pregnancy.**[2,17–26](https://www.nejm.org/doi/full/10.1056/NEJMra2202762" \l "core-r2)**

# Timely syphilis screening and treatment in pregnancy:

<https://jamanetwork.com/journals/jama/fullarticle/1930822>

The odds of congenital syphilis among infants born to mother receiving intervention (to include screening and treatment) in the first and second trimesters of pregnancy compared to the third trimester: odds ratio **2.92, 95% CI 0.66, 12.87. [REF]**

**Risk of congenital syphilis among infants born to mothers with:** Median (IQR) [REF]

* untreated women with syphilis: 34.4% (68.3%–23.7%)
* Treated women with syphilis: 13.9% (21.9%–8.2%)
* Treatment in the first trimester (#12 weeks): **8.2% (9.4%–5.4%)**
* Treatment in the second trimester (12–28 weeks) **19.1% (27.8%–8.7%)**
* Treatment in the third trimester (.28 weeks): **45.0% (60.0%–26.5%)**

Risk of all APOS (adverse outcomes including preterm birth, low birth rate, miscarriage, still birth or fetal loss, neonatal death + congenital ): (Table 6)

* Treatment in the first trimester (#12 weeks): **8.2% (20.6%–6.8%)**
* Treatment in the second trimester (12–28 weeks) **40.0% (63.6%–22.6%)**
* Treatment in the third trimester (.28 weeks): **68.2% (94.4%–34.5%)**

**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 [[1](https://pmc.ncbi.nlm.nih.gov/articles/PMC9879571/" \l "REF1)].
* 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%). [REF]

Let’s think about the intervention we want to model

Reducing proportion of women receiving no screening or late (second/third)

When did you receive

# Target

Diagnosis of PS, EL, Late or unkown: available through Atlas Plus

Individual reports include information on **Primary vs Secondary** diagnosis before 2017 and also diagnosis in STD clinic or non-STD clinic

A table with numbers and a number of people

Description automatically generated

Teritiary syphilis occurs in a third of patients in the absence of treatment (Drago, F.; Ciccarese, G.; Merlo, G.; Sartoris, G.; Parodi, A. Is the Standard Treatment for Early Syphilis Sufficient to Prevent Cardiovascular and Neurologic Syphilis? *Am. J. Cardiol.* **2016**, *117*, 310–311)

## 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.

* 1. Mercuri SR, Moliterni E, Cerullo A, Di Nicola MR, Rizzo N, Bianchi VG, et al. Syphilis: a mini review of the history, epidemiology and focus on microbiota. New Microbiol. 2022;45(1):28-34. Epub 2022/04/12. PubMed PMID: 35403844.
* 2. Kent ME, Romanelli F. Reexamining syphilis: an update on epidemiology, clinical manifestations, and management. Ann Pharmacother. 2008;42(2):226-36. Epub 2008/01/24. doi: 10.1345/aph.1K086. PubMed PMID: 18212261.
* 3. Hicks CB, Clement M. Syphilis: epidemiology, pathophysiology, and clinical manifestations in patients without HIV. UpToDate, Alphen aan den Rijn, Netherlands: Wolters Kluwer <https://www> uptodate com/contents/syphilis-epidemiology-pathophysiology-and-clinical-manifestations-in-patients-without-hiv (Accessed 23 November 2023). 2021.
* 4. Lafond RE, Lukehart SA. Biological basis for syphilis. Clin Microbiol Rev. 2006;19(1):29-49. Epub 2006/01/19. doi: 10.1128/CMR.19.1.29-49.2006. PubMed PMID: 16418521; PubMed Central PMCID: PMCPMC1360276.
* 5. Gross G, Tyring SK. Sexually transmitted infections and sexually transmitted diseases: Springer Science & Business Media; 2011.
* 6. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev. 1999;12(2):187-209. Epub 1999/04/09. doi: 10.1128/CMR.12.2.187. PubMed PMID: 10194456; PubMed Central PMCID: PMCPMC88914.
* 7. Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem. Jama. 2003;290(11):1510-4.
* 8. Oxman GL, Smolkowski K, Noell J. Mathematical modeling of epidemic syphilis transmission: implications for syphilis control programs. Sexually transmitted diseases. 1996;23(1):30-9.
* 9. Gunn RA, Klausner JD. Enhancing the control of syphilis among men who have sex with men by focusing on acute infectious primary syphilis and core transmission groups. Sexually Transmitted Diseases. 2019;46(10):629-36.