

# Unraveling the Enigma of Syphilis: A Comprehensive Review

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## ABSTRACT

*Treponema pallidum* (*T. pallidum*) transmits syphilis through sexual contact or perinatal transmission. *T. pallidum* is widely known for being invasive and immune-evasive; its clinical symptoms are commonly mistaken for those of other diseases due to localized inflammatory responses to multiplying spirochetes. Complement fixation and precipitation/flocculation assays were developed in the early 20<sup>th</sup> century, and they were frequently combined to boost sensitivity and specificity because many cases were challenging. Despite a lifetime of negative anti-lipoidal serology, syphilis sequelae often develop. Treponemal tests (TPI, introduced in 1949) substantially improved sensitivity and reduced the number of false positives, but they were insensitive for primary syphilis. The teaching hospitals in Vienna have long confirmed that the TPHA discovers almost twice as many instances that aren't found as the VDRL. Numerous active cases without VDRL reactions were discovered using the avidity/affinity index (Boltzmann Institute for Serodiagnosis, Vienna) as a substitute for the IgM antibody. Despite these improvements, Ontario's Public Health Laboratory has discovered that gay men who are HIV antibody (+) selectively lose their treponemal antibody, making it hard to detect the incidence of syphilis.

**Keywords:** Syphilis, *T. pallidum*, Treponemal test, Stages, Transfusion.

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## INTRODUCTION

The major source of advice on public health and prevention in the U.S. is the CDC (Centers for Disease Control and Prevention). The CDC has brought together a team of experts in STDs (Sexually Transmitted Disease) for the last four years to provide healthcare professionals with clinical guidance for diagnosing and treating STDs, consulting is the publication of updated STD treatment recommendations.<sup>1</sup>

Girolamo Fracastoro, an Italian physician and poet, coined the term "syphilis" in the year 1530 in the poem "Syphilis sive morbus gallicus" ("Syphilis or the French disease"). The word "Turning thread" is a Greek term that is the source of the genus "Treponema," which refers to one of the oldest human diseases. Mouth, vaginal, anal, and penis transmission routes for syphilis exist. The skin may develop rashes, tiny pimples, or ulcers as syphilis symptoms. Fatigue, itching, mouth ulcers, inflammation of the rectal lining, sore throats and weight loss are additional typical symptoms. In the chronic stage, syphilis is incurable but treatable in the early stages.<sup>2</sup>

## Syphilis

People with syphilis have seen a high risk of HIV-1 (HIV) coinfection ever since the HIV/AIDS epidemic first began.<sup>3</sup> According to CDC data from 2002, 77 times more incidences of primary and secondary syphilis occurred in HIV-infected individuals than in the general population, accounting for 25% of all cases.<sup>4</sup> It is unclear whether early syphilis or neurosyphilis clinical symptoms are worsened by HIV coinfection. HIV patients with CD4+ T cell levels below or equal to 350 cells/mL had an increased risk of developing clinical and CSF abnormalities indicative of neurosyphilis.<sup>5</sup> Even though the prolonged effects of syphilis disease on the prognosis of the HIV-contaminated person are uncertain, one prospective investigation demonstrates that despite brief elevations in CD4+ T cell counts and viral loads, syphilis does not appear to alter HIV advancement. Biological and bacterial factors could be the culprits.<sup>6</sup> Higher rates of co-infection appear with syphilis and HIV. At the same time, high-risk behaviors are to blame for the rising prevalence of syphilis.<sup>5</sup> Doxycycline 100 mg given orally twice daily for 14 days or tetracycline 500 mg given orally four times daily for 14 days might be considered as treatment alternatives for primary or secondary syphilis in cases of penicillin allergy, according to the CDC's 2006 and 2010 STD treatment recommendations. The ideal treatment for all phases of syphilis is parental administration of penicillin G. The 2006 recommendations also included a recommendation for treating primary or secondary syphilis in individuals with penicillin allergies with a single two-gram dose of oral azithromycin. The 2010 updated guidelines warn against



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using single-dose azithromycin due to the emergence of *T. pallidum* strains that are resistant to the drug.<sup>2</sup>

Sexual intercourse can be used to spread the persistent bacterial infection known as syphilis. *Treponema pallidum* is a species of bacteria that causes syphilis. People have been exposed to, treated for, and cured of syphilis for hundreds of years. Therapies are so well established that it was once believed syphilis might be fully eradicated. Despite this, certain American populations are experiencing an increase in syphilis prevalence. In the United States, there were 133945 new cases of syphilis (all stages) in 2020, according to the CDC. Syphilis cases in people with vaginas are rising slightly more than those in those with penises, despite the fact that both groups are witnessing an overall increase in incidence.<sup>7</sup>

It can be difficult to diagnose syphilis. It can take years for someone to experience any symptoms. But the sooner syphilis is identified, the better. Significant harm to vital organs like the heart and brain can result from syphilis that is left untreated for a protracted period. Knowing the signs and causes of syphilis might help you take preventative measures. Knowing about the infection can help you recognize signs and halt the spread of the disease if you do have syphilis. Let's discuss the current standard therapies for syphilis, which is most at risk, and what is known about the disease.<sup>8</sup>

### Causes of syphilis

Syphilis is brought on by a bacterial infection. In 1905, scientists from Germany discovered that the infection was brought on by the bacteria *Treponema pallidum*. The bacterial infection initially exhibits few or no symptoms.<sup>9</sup> The infection spreads over time, affecting several bodily systems, which can have serious consequences.<sup>10</sup>

### Mode of Syphilis transmission

Only direct contact with syphilitic lesions or sores can cause the disease to spread. The mouth, penis, vagina, and anus are the most common places for these lesions to develop. Syphilis is spread through sexual contact, from direct genital-to-genital contact, oral, anal, or vaginal intercourse. Babies exposed to their mother's untreated infection are susceptible to developing syphilis. The medical name for this is congenital syphilis. Syphilis could potentially spread through blood transfusions. However, it's pretty uncommon for that to happen. Contrary to popular opinion, syphilis cannot be inherited. Contrary to popular opinion, syphilis cannot be inherited

Sharing a restroom, Wearing someone else's clothing, Making use of someone else's eating implements, Outside of the human body, syphilis-causing bacteria cannot endure for very long.<sup>11</sup> Transfusion-related syphilis transmission has happened in the past, but it is now considered extremely uncommon thanks to blood supply screening and refrigeration of blood products.<sup>12</sup>

Organ donors who tested positive for syphilis have been documented. Seroconversion has been seen after a deceased donor's liver transplant despite the receiver getting post-exposure prophylaxis.<sup>13-15</sup>

There have been cases of doctors developing extragenital syphilitic sores on their fingers and inside of their noses before it became standard practice for healthcare professionals to wear gloves.<sup>16</sup> In addition, mouth-to-mouth transmission, another method of infection, involves giving babies prechewed food from infected relatives.<sup>17</sup>

## EPIDEMIOLOGY

In 2012, the WHO expected that there will be 17.7 million cases of syphilis among people in the 15-49 age group worldwide, with an estimated 5.6 million new cases occurring year. According to estimates, syphilis incidence and prevalence varied greatly by continent or country, with Africa having the greatest proportion and LMICs making up more than 60% of all new cases.<sup>18</sup> Africa accounts for more than 60% of the estimated worldwide burden of maternal syphilis.<sup>19</sup>

### Who is the most vulnerable to syphilis?

Syphilis can be contracted by anyone. However, certain factors may make you more likely to get an infection. Your risk of contracting an infection could, however, rise in specific circumstances. People in the following categories are at a higher risk of getting syphilis: Those who engage in many partners' sex without using a barrier technique like a condom, Sexual partners for males, Those infected with HIV, and Those who have shared syphilis with others.<sup>10</sup>

### How is syphilis diagnosed?

When someone has syphilis, they should see a doctor immediately and get tested at a nearby health center. A blood sample will be taken by a physician or other healthcare provider to be used for testing and a comprehensive physical examination. If there is a sore, they could collect a sample from it to check for the presence of the syphilis bacterium. A doctor or healthcare provider may recommend a lumbar puncture or spinal tap if a patient has tertiary syphilis-related nervous system issues and positive screening blood tests. Spinal fluid is taken during this surgery so the doctor can do a syphilis bacteria test.<sup>20-22</sup>

### Stages of syphilis infection

#### These are the 4 phases of syphilis

First phase,

Second phase,

Inactive and Third phase.

The most contagious syphilis stages are the first two. Even if syphilis is active in the disguised or latent stage, symptoms frequently do not appear. Tertiary syphilis is the form that poses the greatest risk to health.

### First phase syphilis

Transmission, adhesion, and a localized host immunological reaction. *T. pallidum* is typically spread sexually by tiny skin or mucosal membrane abrasions, and it quickly enters the bloodstream before spreading to other tissues. *T. pallidum* divides at the site of the initial injection once every 30 to 33 hr, resulting in a local inflammatory response. An individual goes through the early stage of syphilis about a month after contracting the bacteria.<sup>23</sup> A chance, a tiny, circular sore, marks the start of it. Even though chancres are painless, they are pretty contagious. Wherever the germs enter the body, such as on or inside the mouth, the genitals, or the rectum, this sore may develop. Small vascular vasculitis results in tissue necrosis and ulceration, and trafficked immune cells generate non-painful regional lymphadenopathy. The chancre cures in 3 to 8 weeks, showing local *T. pallidum* clearance.<sup>24</sup>

Near the initial injection site, *T. pallidum* divides once every 30 to 33 hr, triggering a localised inflammatory response that frequently manifests as a sore three weeks after infection. However, it might take up to 90 days. For two to six weeks, the sore is present. Swollen lymph nodes may occasionally be the only symptom. Direct physical contact with a sore is how syphilis is spread.<sup>8</sup> *T. pallidum*, however, has already systemically disseminated to numerous tissues and organs by this point, preparing the body for the second phase of syphilis.<sup>23</sup>

### Second phase syphilis

Throughout diagnosis and systemic spread, the host immune system responds with motility. *T. pallidum* propels itself by revolves about its long axis using endo flagella that are found in the periplasmic region separating the cytoplasm from the outer membrane.<sup>24</sup> Secondary syphilis symptoms typically start to manifest three months after infection.<sup>25</sup> *T. pallidum* possesses an exterior and inner membrane as well as a periplasmic gap, making it physically comparable to conventional Gram-negative bacteria. Still, it lacks the powerful proinflammatory glycolipid lipopolysaccharide and doesn't result any potent proteins that are currently recognized.<sup>26</sup> Host inflammation and immune system activation are to blame for most syphilis symptoms and tissue damage. Skin rashes and throat pain might be symptoms of the syphilis stage.<sup>27</sup> Although it can form anywhere on the body, the non-itching rash commonly appears on the palms and soles of the feet. Neurological involvement and early CNS invasion.<sup>28</sup> While most individuals with CNS infection by *T. pallidum* seem to control or clear their illness, the causes of some patients' future development of symptomatic neurosyphilis are unknown.<sup>29-31</sup> Some people overlook the rash before it goes away. Headaches,

enlarged lymph nodes, fatigue, fever, facial weakness, weight loss, and visual abnormalities are some other secondary syphilis signs and symptoms that may appear.

Regardless of treatment, these symptoms will go away. However, syphilis still exists in untreated individuals. Secondary syphilis is frequently confused with other illnesses, including Roseopityriasis, lupus planus, and Psoriasis. Because of this, syphilis has earned the moniker "great imitator Trusted Source." It is challenging to identify asymptomatic neurosyphilis due to the absence of CSF tests that are extremely sensitive (CSF-VDRL) or specific (CSF WBC, CSF protein).<sup>32</sup> People may dismiss their symptoms because they might be vague, and professionals may not always be aware that an infection exists.<sup>33</sup>

### Inactive and Third phase syphilis

Antigenic variety and toughness. Due to a host immune response, treponemes persist in many tissues despite a sufficient local clearance of *T. pallidum* from main and secondary lesions, and they do not exhibit any clinical signs or symptoms.<sup>34</sup> As the primary and secondary symptoms disappear, there won't be any visible symptoms. The germs are still present in the body, though. Years could pass between this stage and tertiary syphilis.<sup>20,21</sup> Tertiary syphilis is the infection's final stage. *Borrelia hermsii*, which causes relapsing fever, and *Borrelia burgdorferi*, which causes Lyme disease, are related spirochetes with well-documented antigenic diversity and multistage clinical courses.<sup>20,21</sup> Despite having only a few essential outer membrane proteins, *T. pallidum*. Bioinformatic methods have found several possibilities, including members of the 12 *T. pallidum* repeat (Tpr) protein family.<sup>35</sup> This stage is reached by 14-40% of patients with syphilis. Years or even decades after the initial infection, tertiary syphilis can develop.<sup>36</sup> Tertiary syphilis has the potential to be lethal. Other side effects of secondary syphilis could be blindness, hearing loss, mental health issues, memory loss, and dementia. Destroying bone and soft tissue, Neurological conditions like meningitis or stroke, heart condition, and Brain or spinal cord infection are known as neuro-syphilis.<sup>37,38</sup>

Recombinant TprK vaccination offers some protection from infectious challenges. TprK sequences are highly variable. This variation is limited to seven different protein regions that are thought to be surface accessible. The persistent latent illness may resurface 56 years to a few decades after the initial infection to cause secondary syphilis, which can affect a number of organs.<sup>39</sup> A third of patients with untreated latent syphilis who were studied retrospectively in Oslo during the pre-antibiotic era developed tertiary syphilis. Third-phase syphilis is uncommon, possibly as a result of medicines being mistakenly supplied for other illnesses when treating syphilis.<sup>3</sup>

Different selected diagnoses of genital lesions.

Disease / Disorder	Characteristics of genital part	Virus
Primary syphilis	A single, indurated ulcer that is not painful.	Treponema pallidum
Secondary syphilis	Slightly raised or flat, round or rectangular lumps that are surrounded in a grayish discharge.	T. pallidum
Genital herpes	A collection of tiny, uncomfortable, shallow ulcers with a red base.	<i>Herpes simplex</i> virus.
Chancroid	Embarrassing ulcer with rough edges.	<i>Haemophilus ducreyi</i> .
Venereal warts	Skin-colored or red, velvety pimples that rarely hurt.	<i>Human papilloma</i> virus.
Lymphogranuloma venereum primary stage.	Painless papules, a shallow erosion, or an ulcer.	<i>Chlamydia trachomatis</i> . <sup>40,41</sup>

### Removal of the MTCT for syphilis

Ultimately, the WHO drive to eradicate yaws, which between 1952 and 1964 treated more than failure to treat 50 million individuals with penicillin and reduce the number of illnesses by at least 95% globally.

Unfortunately, as the incidence of yaws decreased, it lost its status as a significant public health issue deserving of a costly vertical program.<sup>42</sup> As a result, resources were moved to other initiatives, yaws were neglected, and they reappeared. Similar circumstances can be found with syphilis; In many areas of the world, the incidence and prevalence of penicillin dropped as it became more widely available, and it lost its position as a top public health concern.

Many areas have had limited coverage; for instance, the WHO estimates that over 50% of African prenatal clinic visitors are not being checked for syphilis. This scenario is worsened by reports of several countries, many of which have a high prevalence of congenital and maternal syphilis, suffer stockouts and deficiencies of injectable benzathine penicillin G.<sup>43</sup> The WHO has been in charge of an assessment of the global supply, present and future demand, and production capacity for benzathine penicillin G.<sup>44</sup> It will take a lot of advocacies to ensure that syphilis control and eradication are prioritized on the global health agenda. As a result of this political resolve and awareness, syphilis MTCT elimination programs, which have lagged for the previous ten

years, will follow in the footsteps of the successful MTCT HIV programs in Africa. For example, the WHO campaign to end the MTCT of syphilis and HIV has a greater understanding of the disease's importance to world health.

To end the MTCT of the illness, the WHO established a target of 50 congenital cases of syphilis for every 100,000 live births in 2014.<sup>45</sup> The approach seeks to provide antenatal care coverage (at least one visit), syphilis testing coverage, and seropositive syphilis treatment to 95% of pregnant women. Congenital syphilis elimination is feasible, as demonstrated by the dramatic drop in HIV-positive children in Africa over the past few years—a more challenging task than lowering the MTCT for syphilis.

POC testing may make screening more accessible for high-risk groups like MSM and FSWs Utilizing communication campaigns, just way it has grown significantly access to screening for pregnant women.<sup>46</sup> Since these tests are carried out outside of a laboratory, the accuracy of the testing must be ensured. For example, according to a study conducted in Brazil's Amazon region, track the progress of healthcare providers in remote places, proficiency panels comprised of dried serum tubes with each healthcare worker evaluated could be employed.<sup>47,48</sup>

### Treatment

A simple penicillin injection is used to treat both primary and secondary syphilis. Syphilis is frequently successfully managed with penicillin, one of the most widely used antibiotics. Another antibiotic, such as Doxycycline, Ceftriaxone, or IV-only penicillin benzothiazide, will likely be used to treat patients with penicillin allergy.

If someone develops neuro-syphilis, they will receive intravenous dosages of penicillin every day. The damage produced by late syphilis cannot be reversed. The main objective of treatment will probably be to lessen agony and discomfort, even though the germs can be removed.<sup>49</sup>

When receiving therapy, be cautious to refrain from sexual activity until all body sores have healed and your doctor has given the all-clear. If someone is sexually active, their partner should also be treated respectfully. Resuming sexual activity should wait until treatment is finished. Treatment for syphilis frequently results in the short-term side effect known as the Jarisch-Herxheimer Reaction (JHR). JHR symptoms may appear within 24 hr of treatment in less than 30% of people with primary or secondary syphilis.<sup>20</sup>

The immune system response is JHR. It causes fleeting symptoms that might range from moderate to severe, such as a headache, fever, chills, a skin rash, GI symptoms including nausea and vomiting, and joint or muscle pain. Typically, JHR symptoms disappear within a few hours.<sup>20</sup>

## How to prevent syphilis

Safe sex practices are the most effective syphilis prevention strategy. When having any sexual contact, use condoms. Additionally, it might be beneficial to:

When having oral sex, use a dental dam (a square piece of latex) or condoms.

Don't distribute sex toys.

Have an STI screening and discuss the results with your partners.

Additionally, sharing needles might spread syphilis. If you use injectable medicines, don't share your hand.<sup>17</sup>

The most efficient method to prevent syphilis is to treat all sex partners immediately to stop reinfection and stop sexual transmission or perinatal transmission from mother to kid. Other Uses of latex condoms, male circumcision, and refraining from having sex with infected partners are all effective prophylactic strategies against the venereal transmission of syphilis.<sup>18</sup>

## Complications associated with syphilis

### *Syphilis can be fatal if left untreated and causes*

Clumps of dead, bloated, fiber-like tissue found in gummas. They are mostly found in the liver. They can also manifest in the skin, bones, eyes, brain, heart, and testis, among other organs. Brain injury, Aneurysm, damaged heart valves, meningitis, paralysis, and aortic inflammatory disease.<sup>49</sup>

## Improved utilization of already available medications

There is an urgent need for oral regimens that are both effective at preventing syphilis from foetal transmission and safe to use during pregnancy.<sup>9</sup> The need for new oral medications is increased by the fact that treatment failure in those with primary syphilis is linked to macrolide resistance. Analyzing current drug combinations could be a valuable strategy to lessen the risk of the emergence of resistance.<sup>19</sup>

## Vaccine Development and Prevention

Syphilis has a highly effective cure, but the disease is nevertheless on the rise in the U.S. and Europe and is currently experiencing an epidemic in China. Creating a vaccine that stops the infection and its spread offers the best chance of controlling the spread of syphilis.<sup>50</sup> According to human challenge investigations, late-latent syphilis patients are resistant to severe reinfection with heterologous strains of *T. pallidum*, and Rabbits were regularly vaccinated with irradiated *T. pallidum*, resulting in the development of protective immunity.<sup>19,51</sup> Failure to successfully cultivate the bacteria *in vitro* has hampered our efforts to develop protective immunity against it. Recent research found that giving rabbits the lipoprotein TP071 vaccination slowed the spread of *T. pallidum*, making it a good option for a vaccine.<sup>52</sup> Discovery

efforts that integrate prospective vaccination targets with diagnostic targets have the potential to advance the development of better means of preventing, controlling, and ultimately curing this disease.

## CONCLUSION

There are numerous ways that syphilis can spread, including sexual contact, vertical transmission, parenteral exposures, and workplace exposures. Syphilis is extremely contagious during primary and secondary syphilis, according to historical research and public health experience. Despite years of syphilis elimination attempts, the rising incidence of the disease in MSM shows how difficult it is to manage the epidemic. It highlights the need for more aggressive and creative prevention methods. The public health system must continue to be vigilant in combating this epidemic to stop the negative effects of syphilis, including severe stages, an elevated risk of HIV transmission and acquisition, vertical transmission, congenital syphilis, and economic costs from hospital stays, treatments, disease examination, and partner services.

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## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**TPI:** Treponemal test; **CDC:** Center for drug control; **VDRL:** Veneral drug research laboratory; **HIV/AIDS:** Human immunodeficiency virus/Acquired immuno deficiency virus; **WHO:** World health organization; **STD:** Sexually transmitted diseases; **STI:** Sexually transmitted infections; **GI:** Gastrointestinal; **MTCT:** Mother to child transfer; **CSF:** Cerebrospinal fluid; **WBC:** white blood cells; **POC:** Point of care testing.

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