

For the Primer, visit [doi:10.1038/nrdp.2017.73](https://doi.org/10.1038/nrdp.2017.73)

→ The spirochaete *Treponema pallidum* causes syphilis via sexual transmission or vertical transmission during pregnancy. Syphilis, despite being easily curable, has persisted — causing several hundred thousand stillbirths and neonatal deaths every year. It has recently re-emerged as a public health threat worldwide.

**MECHANISMS**

*T. pallidum* has a double-membrane structure and endoflagella that provide motility; the bacterium has a flat-wave morphology, replicates slowly and is difficult to culture *in vitro*. Although a local inflammatory response elicited by the bacteria is thought to cause the clinical manifestations of syphilis, how this works is poorly understood. The paucity of surface antigen expression likely enables the spirochaete to be a 'stealth' pathogen and avoid triggering host innate immune mechanisms, facilitating local replication and early dissemination. Sexual transmission of syphilis occurs during sexual contact with an infectious partner with early syphilis (infections <1–2 years in duration). Spirochaetes directly penetrate mucous membranes and, once below the epithelium, *T. pallidum* multiplies and disseminates through the lymphatics and bloodstream; penetration of the blood–brain barrier can eventually cause neurological complications. Neurosyphilis is more common in late syphilis (disease >1–2 years in duration), but can occur in early syphilis.

**SCREENING**

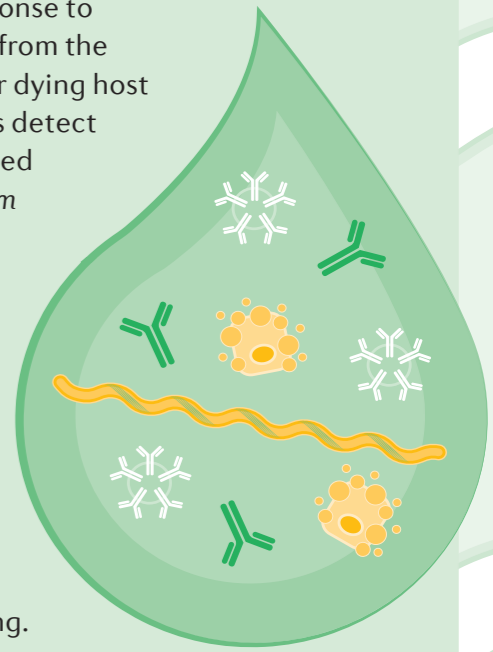
Syphilis screening is universally recommended for pregnant women because of the high risk of mother-to-child transmission

Screening should occur at the first prenatal visit, ideally during the first trimester. Repeat screening in the third trimester and at delivery might identify new infections.



**DIAGNOSIS**

Syphilis can present with painless lesions in the genitals and, later, rashes on the palms and soles — but the manifestations are varied and subtle, leading to many infections being unrecognized. Diagnosis, therefore, requires a suggestive clinical history and supportive laboratory (mainly serodiagnostic) tests. Serodiagnostic tests for syphilis can be broadly categorized as non-treponemal tests (NTTs) or treponemal tests (TTs). NTTs measure antibodies produced in response to lipoidal material from the bacterium and/or dying host cells, whereas TTs detect antibodies directed against *T. pallidum* proteins. Simple rapid tests (needing only a drop of blood) to detect treponemal antibodies have greatly increased coverage of prenatal screening.



A stillbirth should prompt evaluation of the mother for syphilis

Post-delivery, neonates should not be discharged from the health facility unless the serological status of the mother has been determined

**MANAGEMENT**



Women should be tested in each pregnancy. Rapid tests can detect syphilis in low-resource settings.

**EPIDEMIOLOGY**

In 2012, ~17.7 million individuals 15–49 years of age had syphilis. The greatest burden is in Africa, and >60% of new cases occur in low-income and middle-income countries. In these countries, heterosexual spread of syphilis has declined in the general population but remains problematic in female sex workers and their male clients. Men who have sex with men are another high-risk group.

**MANAGEMENT**

Treatment is usually a single intramuscular injection of long-acting benzathine penicillin G, or a course of procaine penicillin. If patients cannot take penicillin, doxycycline (early and late syphilis) or ceftriaxone (early syphilis) can be used. Benzathine penicillin G is the only effective treatment for syphilis in pregnancy and can prevent adverse birth outcomes. *T. pallidum* resistance to penicillin has never been reported.

**OUTLOOK**

A number of issues require attention from the research and policy communities. For example, universal syphilis screening in pregnancy is needed to achieve elimination of mother-to-child transmission. Additionally, HIV and syphilis often co-occur, although how the two infections synergize is poorly understood. Finally, better diagnostic tests to identify active infection, neurosyphilis and congenital syphilis are needed, as is a vaccine.

