Syphilis Screening and Treatment for Pregnant Women

Highlights and Key Messages from the World Health Organization's 2017 Global Recommendations

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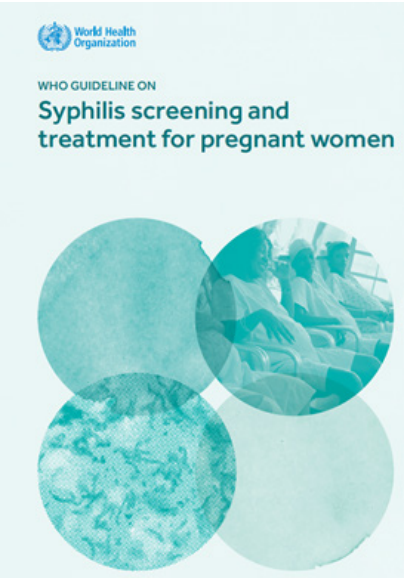
Key Messages

- Syphilis is a bacterial infection caused by Treponema pallidum that results in severe adverse pregnancy outcomes for women and newborns.
- Mother-to-child (congenital) transmission of syphilis is devastating to the fetus; treatment is highly effective if maternal infection is recognized and treated promptly, ideally before the second trimester.
- Advances in syphilis testing, including rapid point-of-care tests, are expanding options for onsite screening and treatment of syphilis in pregnant women.
- The 2017 WHO guideline on syphilis screening and treatment for pregnant women outlines distinct screening and treatment strategies for countries to consider based on a country's syphilis prevalence and health system.
- Achieving and monitoring high coverage and quality of syphilis screening and testing for pregnant women requires regular surveillance, supportive policy, and robust implementation and monitoring strategies.
- To interrupt transmission of infection and prevent re-infection, treating sexual partners is an important component of STI case management.[1]

Background

In 2012, an estimated 357 million new cases of curable sexually transmitted infections (STIs; gonorrhea, chlamydia, syphilis, and trichomoniasis) occurred among 15- to 49-year-olds worldwide, including 5.6 million cases of syphilis. There are an estimated 18 million prevalent cases of syphilis.[1] Syphilis is a bacterial STI caused by *Treponema pallidum* that results in substantial morbidity and mortality. In 2012, an estimated 350,000 adverse pregnancy outcomes worldwide were attributed to syphilis, including 143,000 early fetal deaths/stillbirths, 62,000 neonatal deaths, 44,000 preterm/low-birthweight babies, and 102,000 infected infants.



Syphilis is transmitted through sexual contact (via infectious lesions of the mucous membranes or abraded skin), via blood transfusion, or from a pregnant woman to her fetus. Mother-to-child (congenital) transmission of syphilis is typically devastating to the fetus if maternal infection is not diagnosed and treated early in pregnancy. Table 1 summarizes the four stages of untreated syphilis and the common

[1] World Health Organization (WHO). 2017. *WHO guideline on syphilis screening and treatment for pregnant women.* Geneva: WHO.

signs and symptoms of each stage (primary, secondary, latent, and tertiary). Most untreated primary and secondary syphilis infections in pregnancy result in severe adverse outcomes for the fetus and newborn. Latent (asymptomatic) syphilis infections in pregnancy may cause serious adverse pregnancy outcomes in more than half of cases. The pregnant woman and the fetus can be easily cured with treatment, and the risk of adverse outcomes to the fetus is minimal if the mother receives adequate treatment early in her pregnancy, ideally before the second trimester.

This brief highlights key recommendations from the 2017 *WHO guideline on syphilis screening and treatment for pregnant women* and outlines implementation considerations.

Table 1. Syphilis Stages, Signs, and Symptoms

Stage of Infection	Common Signs and Symptoms	Comments
Primary	Typically presents with painless sore(s) (chancre) at the site of infection on or around the genitals, anus, rectum, or mouth.	May be mild and not noticed. Symptoms typically last 3–6 weeks. Associated with severe adverse outcomes for the fetus and newborn.
Secondary	Typically presents with a skin rash, fever, swollen lymph nodes; rash may appear first on palms of hands or soles of feet but may also appear on trunk and other parts of the body.	May be mild and not noticed. Associated with severe adverse outcomes for the fetus and newborn.
Latent	No signs or symptoms	May cause serious adverse pregnancy outcomes in over half of cases. Without treatment, a person can continue to have syphilis in the body for years without symptoms.
Tertiary	Associated with severe problems of the heart, brain, and other organs.	Tertiary syphilis is severe and can present 10–30 years after a first primary infection (does not develop in all people with latent syphilis).

Background: Syphilis Tests

As noted, *Treponema pallidum* is the bacteria that causes syphilis. Standard laboratory tests for syphilis include non-treponemal (e.g., rapid plasma reagin [RPR], venereal disease research laboratory) and treponemal tests (e.g., *Treponema pallidum* hemagglutination assay, fluorescent treponemal antibody absorption). A presumptive diagnosis of syphilis can be made if one test is positive; a definitive diagnosis of syphilis requires a positive non-treponemal and a positive treponemal test (due to false-positive results). Non-treponemal tests may be negative for up to 4 weeks after a primary infection occurs (women with early primary syphilis usually test positive 4–6 weeks after initial infection). An advantage of quantitative non-treponemal tests (e.g., RPR) is that titres can be used to monitor response to treatment. Titres usually decrease following effective treatment and increase in untreated active infection.

In the past decade, a number of point-of-care rapid syphilis tests (RSTs) have been developed to support point-of-care treatment in settings where follow-up of tested patients is challenging. RSTs provide treponemal antibody results in 10–15 minutes and can be performed on site in any setting, since they do not require refrigerated storage or laboratory equipment (as contrasted with treponemal and non-treponemal serologic tests). A positive RST result, however, does not distinguish between active and previously treated infections and will remain positive even after effective treatment. This poses challenges for screening pregnant women previously treated for syphilis. The different syphilis laboratory tests, laboratory procedures, and interpretation are described in detail in the World Health Organization (WHO)'s *Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus.*[2] Guidance on procurement and information on the WHO list of prequalified in vitro diagnostic products, including a combination HIV/RST option, is available from WHO.[3,4]

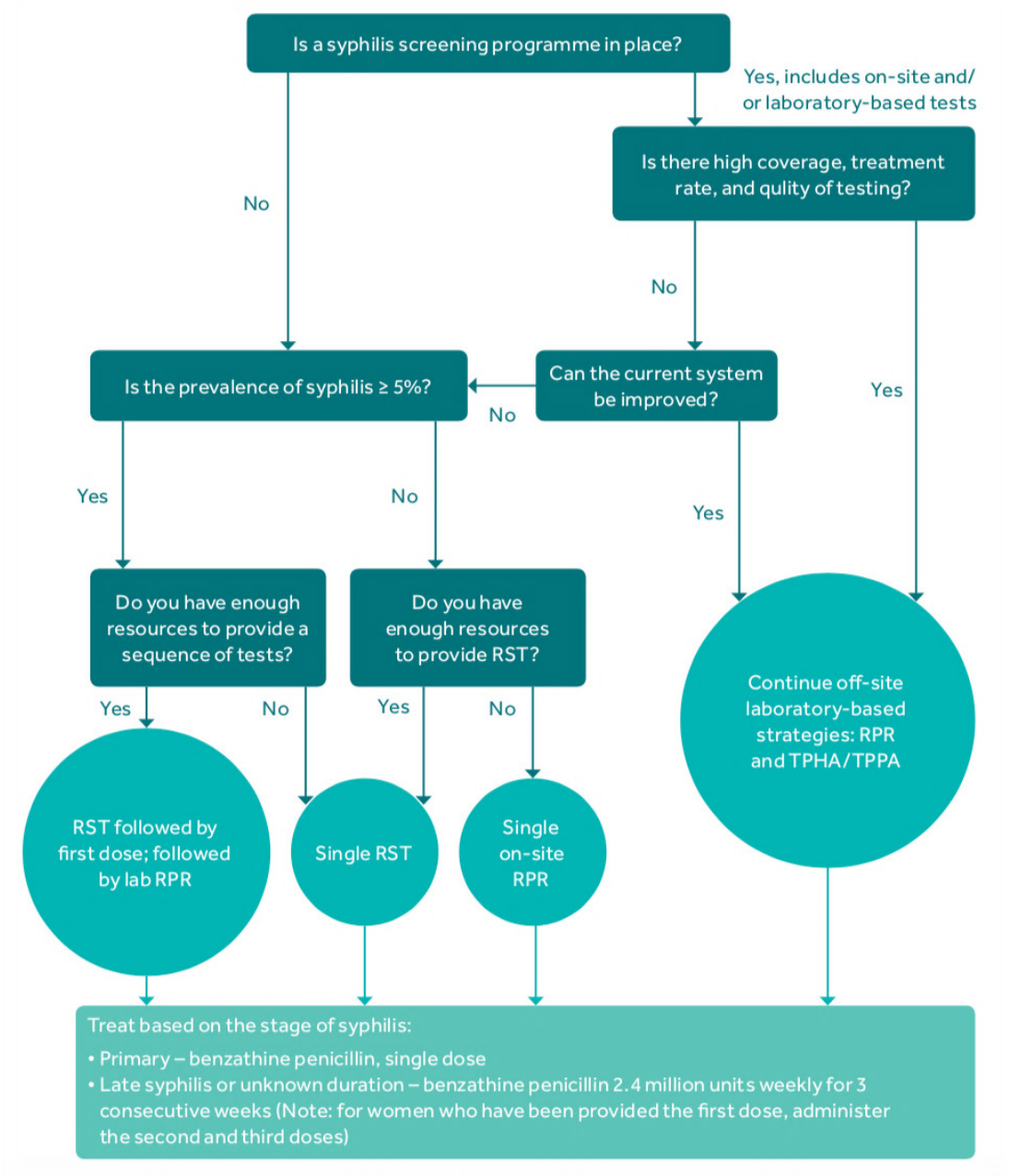
[2] WHO. 2013. *Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus.* Geneva: WHO.
[3] WHO. 2017. *Guidance for procurement of in vitro diagnostics and related laboratory items and equipment.* Geneva: WHO.
[4] WHO. 2018. *WHO list of prequalified in vitro diagnostic products.* Geneva: WHO.

WHO 2017 Screening and Treatment Guideline

Table 2 summarizes the 2017 *WHO Guideline for screening and treatment of syphilis in pregnant women*, including the recommendation that every pregnant woman be screened for syphilis at her first antenatal care (ANC) encounter. These recommendations address syphilis screening strategies in different care settings, the optimal sequencing of tests for syphilis screening, and the treatment of syphilis infections.
The decision to begin a new national syphilis screening strategy that includes treponemal-based RSTs should be based on careful assessment of screening coverage, treatment rate, and quality of the existing testing system (Figure 1). The following points should be taken into consideration.

- **Coverage:** proportion of all people at risk and pregnant women who access syphilis testing
- **Quality of testing:** accuracy of results
- **Treatment rate:** proportion of all people tested who receive results and obtain treatment in a timely manner

Figure 1. Decision-making flowchart for maintaining or introducing new syphilis screening and treatment strategies (2017 *WHO Guideline for screening and treatment of syphilis in pregnant women*)



RST: rapid syphilis (treponemal) test; TPHA: *Treponema pallidum* hemagglutination assay; TPPA: *Treponema pallidum* particle agglutination assay

The WHO 2017 guideline outlines distinct screening and treatment strategies for countries to consider based on a country's syphilis prevalence (less than or greater than 5%) and health system testing capacity.

- In settings with low prevalence of syphilis (< 5%), the guideline recommends a "screen and treat" strategy using a single, onsite point-of-care RST followed by a single treatment dose if positive (Strategy "A").

- In settings with high prevalence of syphilis (> 5%), the guidelines recommend an onsite RST and, if positive, provision of a first dose of treatment and RPR test, and then, if the RPR test is positive, provision of appropriate treatment according to duration of syphilis (Strategy "C").

In every setting with low coverage of syphilis screening and treatment, low laboratory capacity, and poor capacity to follow up with pregnant women, the guideline recommends use of a point-of-care syphilis test over a standard offsite laboratory test.

A syphilis surveillance program can help program managers monitor the national/local prevalence of syphilis to inform the most appropriate screening and treatment strategy in their setting. WHO has developed tools to help countries strengthen surveillance of STI, including syphilis.[5] Syphilis surveillance data can be collected using various methods based on the epidemiological burden and available resources. Universal surveillance refers to surveillance of an entire facility-based population. However, interpreting trends may be challenging due to underreporting, underdetection of syphilis, and fluctuations in care-seeking behaviors. Sentinel surveillance in a subset of facilities is a generally feasible strategy that allows national programs to obtain higher-quality data from a few sentinel sites. However, sentinel sites may not be representative of the population of pregnant women. Stakeholders should weigh the advantages of each surveillance method or potentially a combined method. Stakeholders may also wish to consider intermittent special studies that include syphilis in pregnancy, such as population-based surveys.

Table 2. Recommendations for Screening and Treatment of Syphilis in Pregnancy

Recommendations and Key Considerations	
Recommendation	Key Considerations
Screening for maternal syphilis	
Recommendation 1 The World Health Organization (WHO) sexually transmitted infection (STI) guideline recommends screening all pregnant women for syphilis during the first antenatal care visit.	This recommendation applies to all settings, including settings with high or low prevalence of syphilis.
Screening strategies	
Recommendation 2 In settings with low coverage of syphilis screening and treatment for pregnant women, high loss to follow-up of pregnant women, or limited laboratory capacity, the WHO STI guideline suggests onsite tests (Strategies A, B, and C) rather than the standard offsite, laboratory-based screening and treatment strategy.	These recommendations apply to settings with challenges providing standard offsite laboratory tests and a sequence of tests; the recommendations do not apply to countries that can provide high-quality laboratory-based screening and treatment strategies. When resources do not permit the use of a sequence of tests, a single onsite RST (Strategy A) is suggested to ensure greater screening coverage despite the number of pregnant women who will be overtreated due to the high rate of false-positive results. Provision of onsite RPR requires a rotator, a blood centrifuge, and a refrigerator for reagents, as well as electricity to operate the equipment. RSTs are generally cheaper than RPRs in most settings and do not require refrigeration
Recommendation 3 In settings with a **low prevalence of syphilis** (below 5%), the WHO STI guideline suggests that a single onsite rapid syphilis test (RST) be used to screen pregnant women (Strategy A), rather than a single onsite rapid plasma reagin (RPR) test (Strategy B).	
Recommendation 4 In settings with a **high prevalence of syphilis** (5% or greater), the WHO STI guideline suggests an onsite RST and, if positive, provision of a first dose of treatment and an RPR test, and then, if the RPR test is positive, provision of treatment according to duration of syphilis (Strategy C). The WHO STI guideline suggests this sequence of tests and treatment rather than a single onsite RST (Strategy A) or a single onsite RPR test (Strategy B).	

[5] WHO. 2015. *A tool for strengthening STI surveillance at the country level.* Geneva: WHO.

Recommendations and Key Considerations	
Recommendation	Key Considerations
Treatment recommendations for early syphilis (primary, secondary, and early latent syphilis of not more than 2 years' duration)	
Recommendation 5 In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units IM once.	Treatment is based on duration of syphilis, according to the WHO guideline for the treatment of *Treponema pallidum* (syphilis). Although erythromycin and azithromycin treat pregnant women, they do not cross the placental barrier completely and, as a result, the fetus is not treated. It is therefore imperative to treat the newborn infant soon after delivery (see WHO guidelines for the treatment of congenital syphilis). Ceftriaxone is an expensive option and is injectable. Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications for the fetus or newborn, it is vital that benzathine penicillin always be available in settings that provide care for pregnant women, including antenatal care.
Recommendation 6 In pregnant women with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 million units IM once over procaine penicillin 1.2 million units IM once daily for 10 days. When benzathine or procaine penicillin cannot be used (e.g., due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g., due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 14 days, ceftriaxone 1 g IM once daily for 10–14 days, or azithromycin 2 g once orally.	
Late syphilis (infection of more than 2 years' duration)	
Recommendation 7 In pregnant women with late syphilis (more than 2 years' duration) or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units IM once weekly for 3 consecutive weeks.	The interval between consecutive doses of benzathine penicillin should not exceed 14 days. If the interval between any of the injections exceeds 14 days, then the treatment of three consecutive doses should be restarted. See also key considerations noted above for recommendations 5–6.
Recommendation 8 In pregnant women with late syphilis (more than 2 years' duration) or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units IM once weekly for 3 consecutive weeks over procaine penicillin 1.2 million units IM once a day for 20 days. When benzathine or procaine penicillin cannot be used (e.g., due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g., due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 30 days.	

Implementation Considerations

Effective implementation of the WHO 2017 syphilis screening and treatment recommendations for pregnant women will require the engagement of key actors across system levels, including national policymakers, regional/district managers, facility managers, facility health care workers, community leaders and health agents, and women and families.

National Policy and Training Recommendations

Countries should review and update their policies and standards, as appropriate, to support adoption of the 2017 WHO syphilis screening and treatment recommendations based on a country's syphilis prevalence and health system capacity. Countries should:

- Update national standards and clinical guidelines for STI surveillance, screening, and treatment, including for syphilis, based on WHO's 2017 guidelines.
- Define syphilis screening and treatment competencies for specific cadres of health workers and levels of care, including clear referral guidelines.
- Update training curricula for doctors, nurses, midwives, and other providers who care for pregnant women (e.g., laboratory professionals) based on defined competencies.
- Build health worker clinical skills to recognize symptoms and signs of syphilis, interpret syphilis tests used in the country or subnational context, determine the correct stage of syphilis, treat (or refer) appropriately based on duration of syphilis infection in the pregnant woman, and treat sexual contacts of infected individuals whenever possible.

Program Recommendations

Selected program recommendations for implementing the WHO 2017 guidelines at subnational and service delivery levels are summarized below. These recommendations are not meant to be exhaustive. The strong engagement of district managers and facility health workers who support or provide direct care for pregnant women is essential to identify priority program needs and strategies in the local context.

- Increase provider and community awareness of the benefits of ANC, especially initiation of early ANC in the first trimester, when syphilis screening and treatment yields the greatest benefits; address cultural and health system barriers to ANC access.
- Strengthen supply chain infrastructure to improve national and subnational benzathine penicillin G forecasting, procurement, and distribution to the last mile.
- Support service delivery readiness to implement national strategy for syphilis screening and treatment in pregnancy; readiness includes onsite availability of trained clinical and laboratory staff, practice and referral guidelines, laboratory equipment and testing supplies, infection prevention and control standards, environmental controls for testing kits, availability of benzathine penicillin G for treatment and routine quality assurance measures, etc.
- Build skills of health workers to screen all pregnant women for syphilis at first ANC contact, treat women correctly based on stage of infection, and counsel women effectively on importance of syphilis screening and prevention of syphilis; build health worker skills to appropriately counsel women who test positive on treatment and follow-up, including treatment of sexual contacts of infected people whenever possible.
- Maintain regular quality assurance processes to monitor and ensure accuracy of syphilis tests.
- Establish reliable referral pathways and coordination of specialized care for women with suspected complications of syphilis (e.g., neurosyphilis) and for newborns with congenital or suspected syphilis.
- Engage national obstetrics, laboratory, nursing, and midwifery associations to update members on the new ANC and syphilis testing recommendations, and contribute to discussions on implementation.

Surveillance and Program Monitoring and Learning

ANC programs should define and regularly monitor performance indicators of coverage and quality of syphilis screening and treatment (e.g., percentage of pregnant women screened, percentage of women with positive tests appropriately treated). It is important that ANC facility registers and a woman's ANC record include standard data elements to document syphilis testing results and treatment interventions, including specific dates of testing and treatment. This information is essential to guide effective case management of syphilis infection in pregnant women and to monitor and strengthen program performance.

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