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SPECIAL ARTICLE

Obstetrics

Syphilis in pregnancy: A practical guide for prenatal care providers

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Abstract

Syphilis during pregnancy remains a persistent global public health challenge. Untreated or inadequately treated syphilis infection during pregnancy contributes significantly to preventable perinatal morbidity and mortality. In the last five years, a resurgence of syphilis among pregnant women in several regions has led to a concerning rise in congenital syphilis cases. Vertical transmission can occur at any point during pregnancy or delivery, with the highest risk observed during primary and secondary stages of infection compared to latent phases. To align with the World Health Organization (WHO) target of reducing the vertical transmission rate below 0.05%, the International Federation of Gynecology and Obstetrics (FIGO) has developed evidence-based guidance for the management of syphilis during pregnancy. The guidance advocates for universal early screening, strengthened health systems to ensure access to free and timely prenatal care, and the integration of effective follow-up strategies. As early diagnosis and treatment are highly effective in reducing transmission, syphilis screening should begin at the first prenatal visit. While regional protocols vary, at a minimum, screening should be repeated at delivery in countries that have not yet met WHO eradication targets. Benzathine penicillin remains the treatment of choice, with proven efficacy and safety. Additionally, screening and treatment of sexual partners are essential to prevent maternal reinfection and community transmission. Strengthening health systems to support these interventions is fundamental to improving maternal and fetal/neonatal health outcomes and advancing towards global elimination of congenital syphilis worldwide.

KEYWORDS

congenital syphilis, maternal syphilis, perinatal infection, prenatal care, syphilis management, vertical transmission

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1 | INTRODUCTION

Syphilis is caused by *Treponema pallidum* bacteria and can be acquired through sexual intercourse (oral, vaginal, or anal), blood transfusion, or vertical transmission.[1]

Syphilis infection during pregnancy is a persistent global public health concern. Despite the World Health Organization's (WHO) policy in 2007 on the global elimination of congenital syphilis,[2] the burden of morbidity and mortality due to syphilis continues to persist and in recent years has resurged, affecting both low- and middle-income as well as high-income countries (Figure 1).[4] As such, untreated or inadequately treated syphilis during pregnancy continues to be a significant contributor to preventable perinatal morbidity and mortality.[5] According to the WHO, in 2022, approximately 8 million adults of reproductive age, defined as individuals between 15 and 49 years old, were diagnosed with syphilis globally.[6] In the same year, an estimated 700 000 cases of congenital syphilis were reported, of which approximately 150 000 resulted in early fetal deaths, while approximately 115 000 infants manifested clinical symptoms. Considering that between 50% and 90% of infants are asymptomatic at birth and that initial symptoms might not appear until up to a month later, the true prevalence is likely much higher than currently estimated.[7]

2 | GLOBAL TREND OF SYPHILIS INFECTION DURING PREGNANCY

Many parts of the world are now experiencing a resurgence or increased numbers of syphilis during pregnancy and congenital syphilis cases in the last decade (Figure 2).[3] Global trends are as follows:

- The African and East Mediterranean regions are the most affected, representing 78% of the worldwide burden (Figure 1).
- Two regions have reported an increase in cases of syphilis during pregnancy in the last decade: Eastern Mediterranean and the Americas.
- While Brazil's increasing number of cases accounted for 85% of the cases in South America, the trend for other countries in that region is stable since 2009 but above the WHO's elimination goal (50 cases per 100 000 births). Central America has eight Caribbean countries that achieved the WHO's elimination goal.
- According to the WHO, the United States and Canada both demonstrated a resurgence of syphilis and, therefore, are not included among the 15 countries that have eliminated vertical transmission from 2015 to 2020. In the United States, after a steady decline until 2001, rates started to increase among men and women, and in 2021, congenital syphilis reached the highest rate in three decades.[8] There is also a current epidemic of congenital syphilis in Canada, particularly in Western Canada.[7]
- South-East Asia has experienced a decrease as the Western Pacific region had remained stable in the last decade.
- The European region contributes the least to the global burden (0.3% in 2016).

3 | VERTICAL TRANSMISSION: IMPACT OF STAGE OF SYPHILIS AND TREATMENT TIMING

Vertical transmission can occur during pregnancy or at the time of delivery, with the risk of transmission increasing significantly during primary and secondary syphilis compared to latent syphilis (Figure 3). Congenital syphilis can occur in any stage of maternal infection during pregnancy and is associated with preterm birth and perinatal death. Screening and treatment timing are crucial for reducing the risk of transmission. Many studies demonstrate that the earlier treatment is administered, the more likely it is to decrease the risk of congenital syphilis and adverse pregnancy outcomes

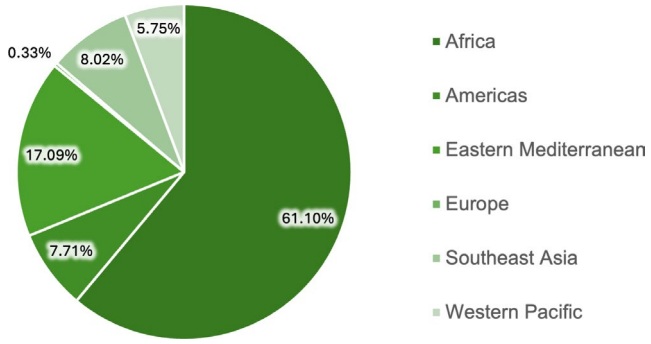


FIGURE 1 Estimated global burden of congenital syphilis by region in 2023.[3]

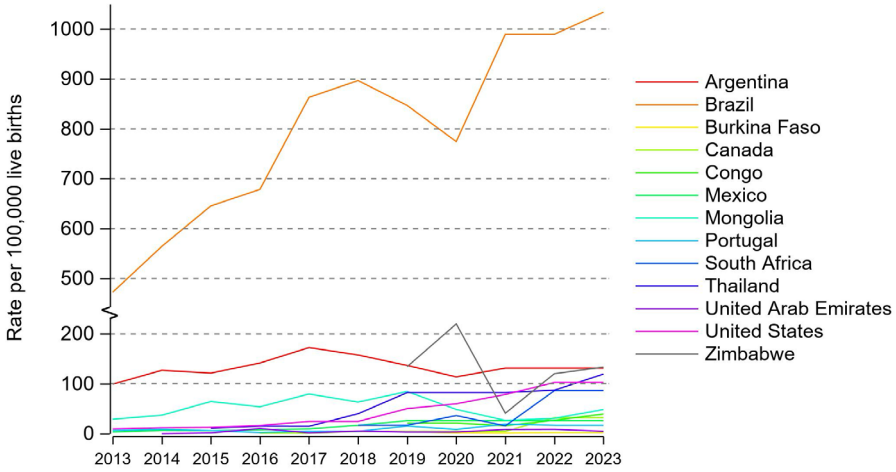


FIGURE 2 Congenital syphilis reported rate per 100000 live births from 2013 to 2023. This graphic illustrates the trend of congenital syphilis cases until the most recent data collection (2023) by WHO. Missing data points have been filled with the values from the previous recorded year to maintain continuity in the trend line.

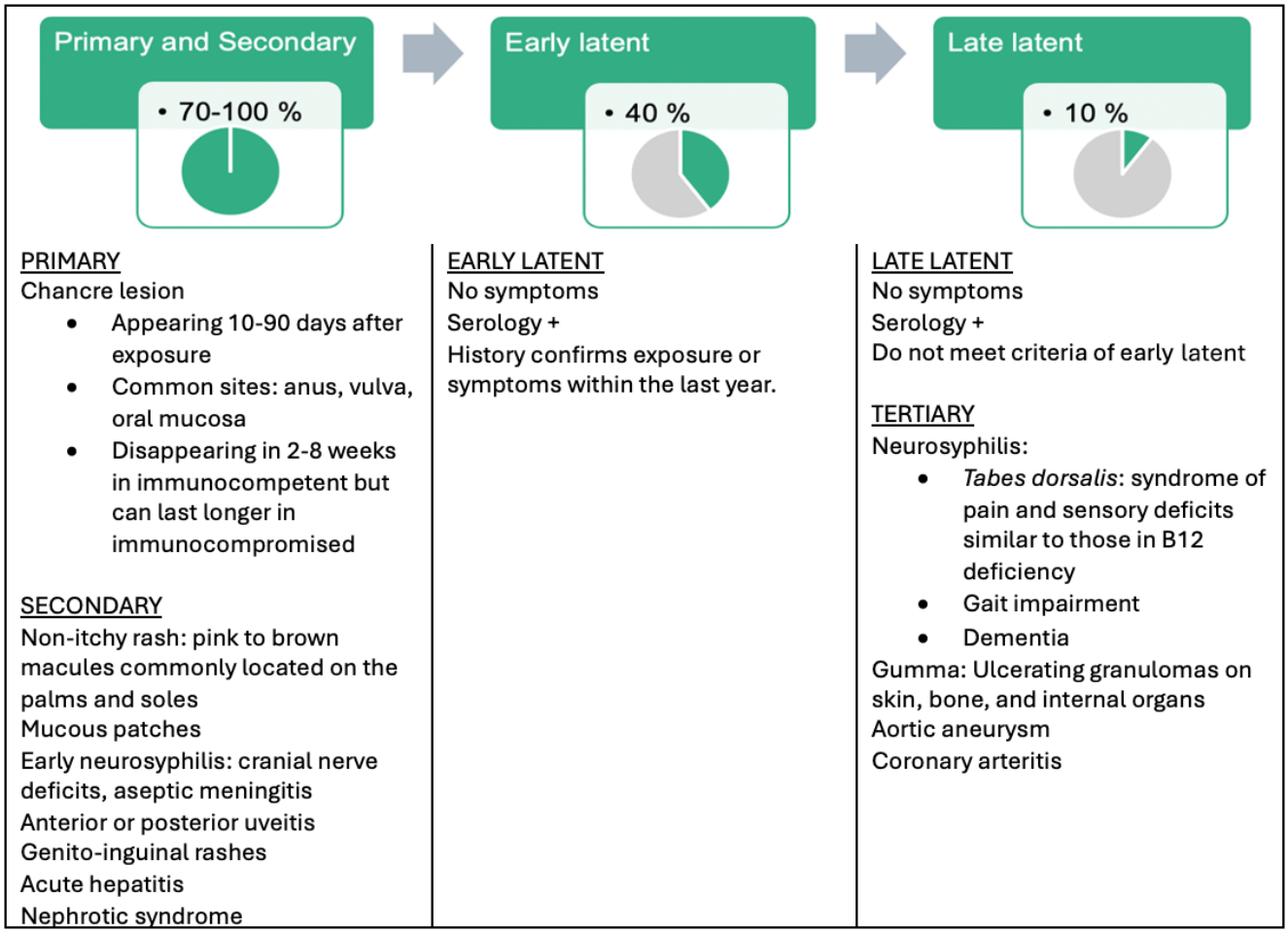


FIGURE 3 Vertical Transmission Risk According to Syphilis Stage.[9–11]

(Figure 4).[12–15] The risk is nearly eliminated when appropriate treatment is completed during the first trimester.[15] Completing treatment in the first or second trimester significantly reduces the risk of congenital syphilis compared to treatment in the third trimester.[16] Screening and treatment timing are crucial for reducing the risk of transmission.

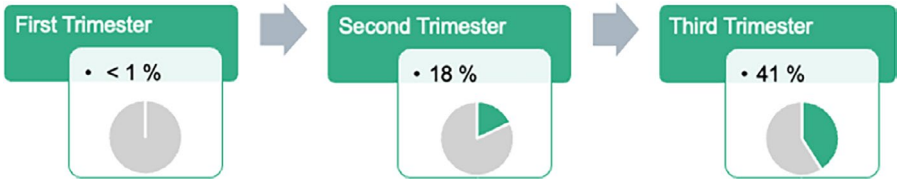


FIGURE 4 Vertical Transmission Risk According to Treatment Timing in Pregnancy.[12–15]

TABLE 1 Interpretation chart for the serodiagnosis of syphilis.[17]

Result of serological test			
TT	**NTT**	**Confirmatory test (TT)[a]**	**Possible interpretation**
N/A Nonreactive	Nonreactive N/A	N/A	1. No treponematosis (no syphilis) 2. If incubating syphilis is suspected, obtain a 2nd specimen 3 months after the presumed exposure 3. If PRIMARY syphilis is suspected, obtain a 2nd specimen 2–4 weeks after symptom onset, consider NAAT and/or IgM 4. IF SECONDARY syphilis is suspected, notify the laboratory to assess the possibility of a prozone phenomenon[b] (false-negative NTT when titers are very high)
N/A Reactive Reactive	Reactive (all titers) Reactive (≥1:8) Reactive (titers 1:1 to 1:4)	Reactive N/A Reactive or not necessary	1. Syphilitic treponematosis.[c] The clinical presentation and treatment history must be ascertained in order to provide greater certainty in the interpretation: a. EARLY syphilis: PRIMARY, SECONDARY or EARLY LATENT b. LATE LATENT syphilis c. TERTIARY syphilis 2. Treated syphilis with persistent reactive RPR (NTT 1:1 to 1:4)
Reactive	Nonreactive	Reactive	1. Syphilitic treponematosis.[c] The clinical presentation and treatment history must be ascertained in order to provide greater certainty in the interpretation: a. PRIMARY syphilis before NTT seroconversion b. SECONDARY syphilis with prozone phenomenon1 in the NTT c. LATE LATENT syphilis after NTT seroreversion 2. Treated syphilis 3. Possible nonsyphilitic treponematosis (bejel, yaws or pinta)
N/A Reactive	Reactive (all titers) Nonreactive or reactive (titers 1:1 to 1:4)	Nonreactive	1. No treponematosis (false positive). 2. If incubating syphilis or PRIMARY syphilis is suspected, obtain a 2nd specimen 2–4 weeks later

Note: For further information, see the syphilis serodiagnostic algorithms. The table is reproduced with permission from INESSS 2023, Pharmacological treatment of STBBI—Syphilis, licensed under CC-BY (accessed at https://www.inesss.qc.ca/fileadmin/doc/INESSS/Outils/Guides_ITSS/ITSS_Syphilis_WEB_EN.pdf).

Abbreviations: N/A, not applicable (not performed); NAAT, nucleic acid amplification tests; NTT, non-treponemal test; TT, treponemal test.

[a]Defer to local laboratory indications.

[b]Prozone phenomenon: a specimen with a high antibody titer might result in a false-negative NTT response when the serum is not diluted.

[c]This disease must be reported to public health authorities.

4 | SYPHILIS TESTING

4.1 | Serology

Serologic screening is the most efficacious strategy to identify and treat syphilis because clinical diagnosis can be difficult, as symptoms and signs might mimic other diseases, be undervalued, or not perceived. A guide for syphilis serological interpretation is provided in Table 1.[17]

The choice of algorithm should be based on available laboratory resources, test volume, and patient populations served. In the laboratory-based reverse sequence algorithm, a treponemal test (automated treponemal enzyme immunoassay or chemiluminescence assay) is used first, followed by a quantitative non-treponemal test (Figure 5).[18] Because treponemal tests remain positive after previous syphilis, even if adequately treated, the ideal strategy recommends performing a treponemal test followed, if positive, by a non-treponemal serological test to confirm syphilis. This strategy should

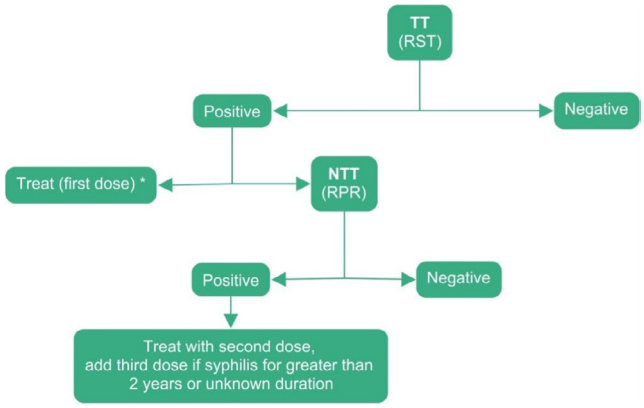


FIGURE 5 WHO's Syphilis reverse testing strategy with Laboratory Support to inform treatment.[18] This algorithm begins with a treponemal test (TT), like the rapid syphilis treponemal (RST) test; if this initial test is positive, it advises proceeding to a non-treponemal test (NTT), like the rapid plasma reagin (RPR). *In certain regions, the NTT can be conducted rapidly and automatically if the TT is positive, allowing us to wait for the results of both tests before treatment. If delays are expected in obtaining NTT results, it is recommended to treat based solely on the positive TT—provided there is no prior history of treated syphilis.

be preferred only if quick results and, if positive, rapid follow-up visits of pregnant women are guaranteed. A patient with reactive results on both treponemal and non-treponemal tests should be considered infected unless prior treatment results in a decrease by a factor of 4 from the pretreatment non-treponemal titer is appropriately documented, maintaining a stable low titer for non-treponemal test, and no concern about reinfection.[8] In cases where there are delays in obtaining non-treponemal test results, treatment based solely on the positive treponemal test is recommended, provided there is no prior history of treated syphilis.

4.2 | Point-of-care testing

In settings with low coverage of laboratory-based screening, point-of-care treponemal rapid tests are recommended by the WHO.[19] Having a positive point-of-care test is sufficient to start treatment, a strategy recommended to reduce the risk of losing the opportunity to prevent transplacental transmission and congenital syphilis.

Treponemal rapid tests can also be used as the entry point for the reverse algorithm, followed by laboratory-based testing, to speed up diagnosis and treatment in regions with high prevalence of syphilis among pregnant women.

4.3 | Nucleic acid amplification tests

Because antibodies might not develop for 2–4 weeks after infection (some might take up to 90 days), there is a chance of false-negative serology during early infection. Nucleic acid amplification tests on a swab of lesion or lesion exudate have excellent sensitivity and specificity. They can be used for primary or possible secondary syphilis lesions (e.g., moist lesions, including genital and oral lesions),[20] but it is costly and not easily available. It can also be used in amniotic fluid or neonatal blood to facilitate the diagnosis of congenital infection.

4.4 | Immunoglobulin gM detection

The first class of immunoglobulin to respond after a recent infection is immunoglobulin (Ig) M. Early detection of IgM could, therefore, help with the diagnosis of early syphilis. As its main function is to assess syphilis status in newborns and cephalo-spinal fluid, it can help to detect early syphilis infection during pregnancy if available.[21]

5 | DIAGNOSING SYPHILIS INFECTION DURING PREGNANCY

Even if infection is frequently identified through routine screening during pregnancy, recognizing clinical manifestations is crucial for timely intervention. As illustrated in Figure 3, early symptoms might include painless sores or ulcers at the site of infection, which are characteristic of the primary stage of syphilis. As the disease progresses, secondary symptoms can manifest as rashes, fever, swollen lymph nodes, and sore throat, among others. Understanding these signs and symptoms enables healthcare providers to swiftly identify potential cases of syphilis and initiate appropriate testing and treatment, ultimately reducing the risk of complications and transmission. Additionally, all cases of intrauterine fetal demise/stillbirth should be investigated for syphilis.

5.1 | Prenatal fetal signs of congenital syphilis

Congenital abnormalities, such as hepatomegaly, splenomegaly, bowel abnormalities, fetal growth restriction, ascites, hydrops, and elevated middle cerebral artery peak systolic velocity are common features observed by prenatal ultrasound in cases with congenital syphilis[22] and should trigger syphilis serological testing. Absence of ultrasound abnormalities does not exclude congenital infection as up to 70% of the cases are asymptomatic.[23] Note that the treatment of syphilis during pregnancy aims to resolve fetal symptoms, notably hydrops.[23]

6 | CURRENT SCREENING STRATEGIES DURING PREGNANCY AROUND THE WORLD

It is widely accepted that screening should be started during the first prenatal visit. Nevertheless, repeating serology for syphilis during

pregnancy differs across countries and within regions.[24] Many studies emphasize the advantages of conducting serological screening during the first or second trimester.[15,25–27] In the WHO recommendations on antenatal care for a positive pregnancy experience guideline,[28] syphilis screening should be made at the first prenatal care visit, ideally before 12 weeks of gestation. Access to early first screening is highly linked to universal and free prenatal care.[29,30]

The number and timing of follow-up screenings during pregnancy remain a topic of debate because prior infection with syphilis does not confer immunity. Between 11% and 78% of congenital syphilis cases are related to a new syphilis infection during pregnancy despite negative syphilis screening at the first antenatal visit.[16,31–35] Therefore, repeat syphilis screening in the second/third trimester and/or at delivery is recommended if prevalence is high or increasing, allowing timely identification and treatment, then follow-up of intrauterine-exposed newborns.

In certain countries and territories, the decision to repeat syphilis screening during pregnancy hinges on the presence of risk factors, which can be challenging to identify.[24] The definition of a population or at-risk environment varies significantly, as does the list of behavioral factors that might increase an individual's susceptibility to contracting syphilis. Client openness and ability to share risk factors might be limited. Moreover, effectively identifying these risk factors relies on healthcare professionals' knowledge, expertise, and observational skills, enabling them to accurately detect and address potential community vulnerabilities.

The intensity of the screening strategy should be tailored to align with local and national syphilis epidemiology. A more intensive approach is warranted in areas with high or rising incidence rates. At the same time, a strategy based on symptoms and risk factors might be suitable for regions with stable and low incidence. For instance, in the UK, where new infections during pregnancy are expected to be 0.0017% of pregnancies, repeating screening at late pregnancy is not cost-effective,[36] while in the USA, it would be cost-effective if the prevalence was 0.17%.[37] The WHO strongly recommends including screening at the first prenatal visit, repeating at the transition from the second to third trimester, during the delivery of a livebirth, and, even more importantly, at the time of a stillbirth.[38,39] This protocol is similar for some countries,[40] while others reinforce its application in regions with a growing epidemic.[7]

7 | CONSIDERATION REGARDING TREATMENT OF SYPHILIS DURING PREGNANCY

No other drug besides penicillin is considered effective and safe for use during pregnancy as it is shown in Table 2. However, shortages of benzathine penicillin G have been reported, prompting a search for alternative treatment options. If benzathine penicillin G is scarce at a national or regional level, priority should be given to treating pregnant women because other options do not treat the fetus. If benzathine penicillin G is not available, ceftriaxone might be an option.[41]

The Jarisch–Herxheimer reaction (fever, chills, myalgia, headache, tachycardia, hyperventilation, flushing, or mild hypotension) has been described in 8%–56% of people treated for syphilis within 24 h post treatment, especially in the context of secondary syphilis.[42] This reaction can be associated with threatening preterm labor in pregnant person above 24 weeks of gestational age.[43]

8 | FIGO COMMITMENTS

Prenatal care providers and health services have a substantial responsibility in controlling congenital syphilis by proactively reaching out to pregnant women for screening and treatment. Commonly missed opportunities for prevention include late or no prenatal care, inadequate or no maternal treatment, no testing at all, and late pregnancy seroconversion.[44]

Education of healthcare professionals plays a crucial role in preventing maternal and congenital syphilis. It ensures accurate diagnosis and appropriate management of syphilis in pregnant women, including prompt treatment to prevent transmission to the fetus. For instance, Caitano et al. (2022) analyzed the impact of a massive open online course (MOOC) learning pathway, “Syphilis and other STIs” on the response to the syphilis epidemic in Brazil.[45] The course consisted of 54 MOOCs designed to improve healthcare professionals' knowledge and practices regarding syphilis. The study concluded that the MOOC was a successful strategy to address the syphilis epidemic in Brazil, contributing to improved health outcomes and aligning with national and global health priorities. Therefore, FIGO is committed to:

- Developing evidence-based guidelines for the management of maternal syphilis and to supporting healthcare providers in delivering optimal care;
- Supporting WHO's goal of eliminating maternal syphilis, by encouraging every country to reinforce their syphilis screening strategies in pregnant women;
- Promoting access to syphilis screening during pregnancy, which is facilitated by free prenatal care.

9 | FIGO RECOMMENDATIONS

9.1 | Syphilis screening and testing

- Syphilis initial screening should be performed during the first trimester for every pregnant woman, preferably at the first antenatal visit (Figure 6).
- Syphilis screening should be mandatory at delivery, regardless of the presence of risk factors, to allow for the identification of cases of congenital syphilis due to infection or reinfection during pregnancy in countries that did not achieve the WHO eradication objective (Figure 6).
- Depending on the incidence rate of syphilis, an intermediate screening around 28 weeks of gestation should be considered (Figure 6).

- The screening based on the reverse strategy, with on-site rapid tests where available, is a strong recommendation if the prevalence or access to laboratory services is scarce.
- Any pregnant person with any sign or symptom of syphilis should be tested regardless of gestational age.
- Testing the pregnant person is strongly recommended in cases of stillbirth/fetal demise.
- A pregnant person with a positive test for syphilis should be offered screening for other sexually transmitted infections.

9.2 | Syphilis treatment and follow-up

- Treatment with benzathine penicillin should be started as early as possible after screening results (Table 2).
- Because penicillin is the only proven antibiotic effective for treating syphilis, the recommended first-line therapy is injectable penicillin, with the number of doses depending on the stage of the infection (Table 3). Penicillin is effective in curing syphilis during pregnancy, but more research is needed on the best dosage and duration of treatment for early syphilis.[47]
- The most recommended treatment is one dose of benzathine penicillin G 2.4 MU IM for early syphilis (primary, secondary, or early latent stages) and three weekly doses (total 7.2 MU) for late latent syphilis or with unknown duration.
- In the case of suspected penicillin allergy, challenges might be appropriate depending on the type of reaction and how long ago it occurred.[48] If an allergy is proven, desensitization is recommended.
- If benzathine penicillin G is not available, other options are described in Table 2.[41]
- Symptoms of the Jarish–Herxheimer reaction should be known by the patient. While there is no specific treatment for it, management should include fever/pain relief (e.g., paracetamol) and hydration, according to local guidelines and protocols.
- Management of syphilis should be undertaken by the prenatal care provider, supported if needed by a specialized team.
- Ideally, ultrasonography should precede antepartum therapy to detect fetal complications such as hydrops. However, treatment should never be delayed to wait for this exam.
- Pregnant women should be followed using a non-treponemal titrated test monthly to guarantee the treatment was effective or identify failure, inadequate treatment, or reinfection (Table 3).
- A fourfold reduction or at least two dilutions lower titer after 3–6 months is considered an adequate response to treatment.[49] It is important to note that a recent study showed a slower reduction of non-treponemal test titer among pregnant women.[50]
- Newborns from women diagnosed with syphilis should be adequately evaluated by testing for their RPR and undergoing a clinical examination looking for features of congenital syphilis. Further investigations and treatment, if needed, should be

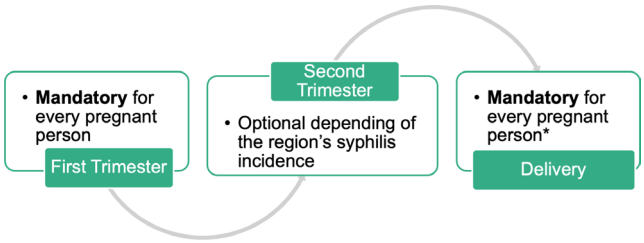


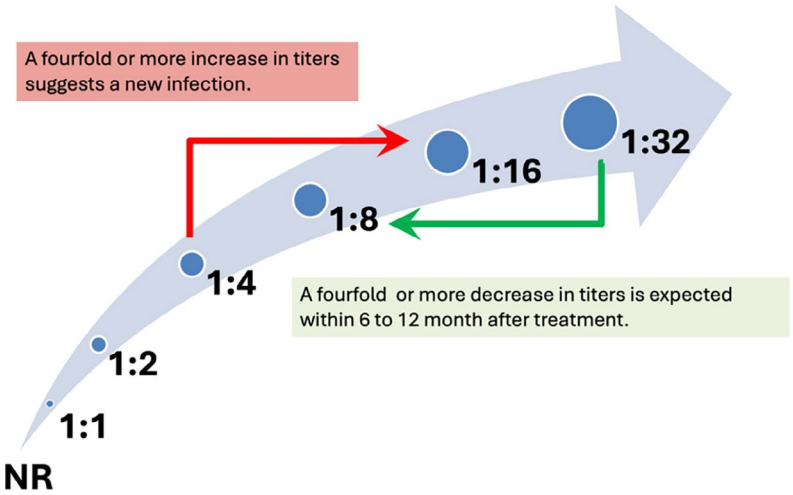
FIGURE 6 Calendar of Prenatal Syphilis Screening. *In countries that did not achieve WHO eradication objectives, as well as in stillborn events.

TABLE 2 Syphilis treatment during pregnancy.

	Primary, secondary, and early latent syphilis	Late latent syphilis or unknown stage
Recommendation number1	Benzathine penicillin G 2.4 million units once intramuscularly	Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks
Recommendation number 2	Benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once daily for 10 days	Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units intramuscularly once a day for 20 days
Recommendation number 3	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), use ceftriaxone 1 g intramuscularly once daily for 10 days. Doxycycline might be an alternative if penicillin or ceftriaxone is unavailable, supported by a shared decision on uncertainties, including adequate doses, safety and prevention of congenital syphilis. The dosage should be 100 mg per dose two or three times per day for 14 days	When benzathine or procaine penicillin cannot be used (e.g., due to penicillin allergy where penicillin desensitization is not possible) or are unavailable (e.g., due to stock-outs), use erythromycin 500 mg orally four times daily for 30 days Congenital syphilis was described after the use of macrolides as erythromycin due to resistance or because they do not cross the placental barrier completely. If erythromycin is used, treating the newborn infant is necessary

Note: This table outlines the World Health Organizations (WHO's) recommendations[18] for the treatment strategies for syphilis infection during pregnancy. It also incorporates specific treatment protocols validated and adjusted based on recent studies.[41,46] Adapted from WHO 2017, WHO Guideline on Syphilis screening and treatment for pregnant women, under CC-BY license (https://iris.who.int/bitstream/handle/10665/259003/9789241550093-eng.pdf?sequence=1).

TABLE 3 Serological follow-up by quantitative non treponemal test after treatment during pregnancy.

Timing of syphilis serology[a]	Example of the evolution of NNT titers and their interpretation
• At the beginning of treatment (establishing titer baseline) • Monthly until a negative test or plateau is reached • At 28 weeks • At delivery • One year after treatment	

Note: Titers may fluctuate slightly (one dilution) but should still show an overall downward trend post-treatment.

Abbreviation: NTT, non-treponemal test; NR, non-reactive.

[a]The same test and laboratory should be used for all follow-ups.

informed by pediatric experts in this area (see the WHO's treatment guidelines for congenital syphilis: https://iris.who.int/bitstream/handle/10665/249572/9789241549806-eng.pdf?sequence=1).[51]

9.3 | Management of partner(s)

- The presence or absence of intimate partners should always be addressed to ensure they receive appropriate treatment. If bringing partners for screening and counseling is not realistic, treatment can be recommended.
- The use of procaine penicillin, doxycycline, or ceftriaxone should only be considered when benzathine penicillin G is unavailable or in case of severe allergy.

9.4 | Other considerations

- Sexual intercourse should be avoided until full treatment has been completed. In addition, the resumption should be according to the partner's status and, if applicable, their treatment.
- Use of protection (condom) during sex is recommended after treatment, to avoid reinfection.
- Report diagnostics of syphilis to public health authorities as required by local regulation.

AUTHOR CONTRIBUTIONS

AAD: Investigation, writing—original draft preparation and finalizing of the manuscript. EA, JM, DP, MLM, EB, DA, DM: Resources, writing, reviewing and editing. IB: Conceptualization, project administration, resources, supervision, writing, reviewing, editing, and finalizing of the manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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