Maternal-to-Fetal Transmission of Syphilis and Congenital Syphilis

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PRACTICE GAPS

Worldwide, congenital syphilis affects 1 million births and leads to 200,000 fetal and neonatal deaths each year. Cases of congenital syphilis have been on the rise in the United States and neonatal clinicians need to be cognizant of the risk of maternal-to-fetal transmission, approaches to screening pregnant women for syphilis, and the evaluation and treatment of potentially affected neonates.

OBJECTIVES *After completing this article, readers should be able to:*

1. Explain maternal-to-fetal transmission of syphilis, including the epidemiology of acquired syphilis, effect on birth outcomes, stages of acquired syphilis, and screening, treatment, and prevention in pregnant women.
2. Describe congenital syphilis, focusing on the epidemiology, pathology, clinical presentation, diagnosis, treatment, prognosis, and follow-up.

ABSTRACT

Between 2012 and 2018, rates of congenital syphilis increased by 291% in the United States. In 2018, the rate of congenital syphilis was the highest it has been since 1995. Given these concerning epidemiologic trends, this review seeks to summarize the maternal-to-fetal transmission of syphilis to ensure adequate care of affected mothers and their infants. It also serves as a call to reinvest public health resources and reestablish infrastructure to ensure reversal of this concerning trend to stop preventable perinatal deaths, associated morbidities, and long-term consequences of congenital syphilis.

INTRODUCTION

Worldwide, 1 million pregnant women are affected by syphilis, resulting in 661,000 cases of congenital syphilis and 200,000 fetal and neonatal deaths each year. (1)(2) Syphilis is the second leading cause of stillbirth in the world. (3) In the United States, rates of syphilis among women of reproductive age and correspondingly, rates of congenital syphilis, have been increasing since 2012. (4) This is concerning because maternal-to-fetal transmission of syphilis not only leads to fetal and perinatal deaths, but also

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ABBREVIATIONS

AAP	American Academy of Pediatrics
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CSF	cerebrospinal fluid
HIV	human immunodeficiency virus
PCR	polymerase chain reaction
RPR	rapid plasma reagin
WHO	World Health Organization

to prematurity, low birthweight, and congenital syphilis. Although the majority of neonates with congenital syphilis are asymptomatic at birth, this infection may present with a wide range of signs and symptoms, resulting in significant morbidity, particularly long-term neurologic and developmental consequences. Because syphilis can be effectively and inexpensively treated with penicillin, congenital syphilis should be mostly preventable with adequate public health policies and infrastructure that provide accessible and adequate prenatal and neonatal care.

EPIDEMIOLOGY

Epidemiology of Acquired Syphilis in the United States

The United States began reporting syphilis rates in 1941 and with the introduction and dissemination of penicillin by the 1950s, rates of syphilis initially fell rapidly and steadily (Fig 1). This was true until the late 1980s to early 1990s when there was an increase in syphilis rates attributed to the crack cocaine epidemic, prostitution, and lack of public health resources. (5) With renewed investment and commitment to controlling syphilis, rates began to decline again in the early 1990s and reached the lowest rates ever reported in the United States in 2000 and 2001 (2.1 cases/100,000 population). (4) However, syphilis rates have been steadily increasing since 2001 and have essentially made gains every year since that time. In 2018 (the most recent year for which data are available), the total case count of all stages of syphilis was the highest it has been since 1991 and the rate of primary and secondary stages of infection (the most infectious stages) was 10.8 cases/100,000 population (total of 35,063 cases). (4) The 2018 increases occurred among men and women in all regions of the United States and all racial and Hispanic ethnicity groups. The increases over the last 20 years were initially caused by

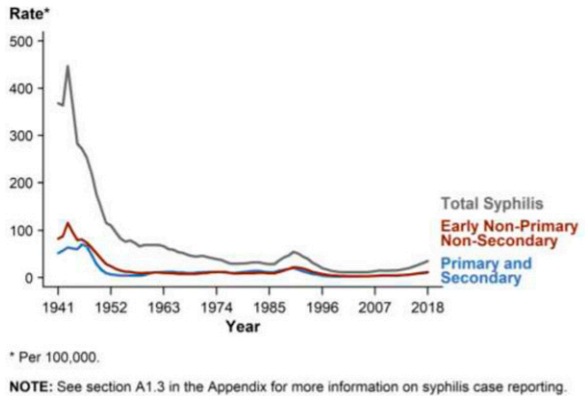


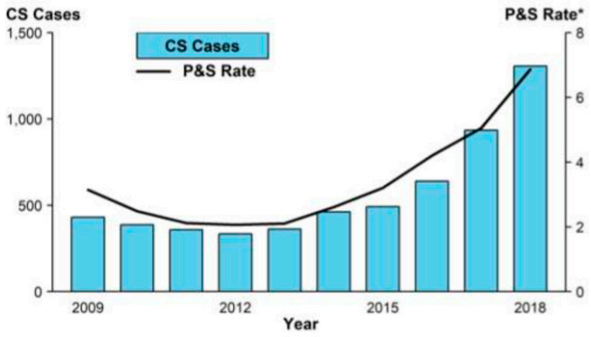
Figure 1. Syphilis cases reported from 1941 to 2018. From Centers for Disease Control and Prevention. Syphilis: CDC Fact Sheet (Detailed). https://www.cdc.gov/std/syphilis/stdfact-syphilis-detailed.htm. (6)

increased rates among men who have sex with men only (who continue to have the highest rates of syphilis), followed by men without data on sex of partners and men who have sex with women only; however, since 2014, the rate among women has almost tripled. (4) From 2014 to 2018, the rate of primary and secondary syphilis among women increased 172.7% (from 1.1 to 3.0 cases/100,000 women) and among women during reproductive (15–44 years) increased 165.4% from 2.6 to 6.9 cases/100,000 women. (4) Among women, the highest rates of primary and secondary syphilis are in those of childbearing years, with the highest rates in those aged 20 to 24 years, followed by 25 to 29 years and 30 to 34 years. (4) Although there is variability by state, in 2017–2018 the rates of syphilis among women increased in every region of the United States and were highest in the western and southern regions. (4)

Epidemiology of Congenital Syphilis in the United States

The epidemiology of congenital syphilis usually tracks along that of primary and secondary syphilitic disease in reproductive age women. After a steady decline, congenital syphilis also peaked in 1991 at 100 cases in 100,000 live births, related to the increase in overall syphilis rates and rates among women during the late 1980s to early 1990s. (5) Though this was partially related to true increases in rate, it was also caused by a definitional change in the criteria for congenital syphilis. Congenital syphilis rates then declined from 1991 to 2005, underwent a slight increase from 2005 to 2008, and declined again from 2008 to 2012 to 8.4 cases in 100,000 live births. (4) However, since 2012, rates of congenital syphilis have increased every year (Fig 2). In 2018, the rate of congenital syphilis was 33.1 cases in 100,000 live births, a 291% increase from 2012 and the highest rate of congenital syphilis since 1995. (4) In 2018, there were 1,306 cases of congenital syphilis, which resulted in 78 stillbirths and 16 deaths. (4) The increases in congenital syphilis rates between 2014 and 2018 have mostly been attributed to increasing rates in the western (48.5 cases/100,000 live births in 2018) and southern (44.7 cases/100,000 live births in 2018) United States. (4) Cases were highest among infants of mothers who were black, followed by Hispanic and white. (6)

Risk factors for congenital syphilis include lack of or inadequate prenatal care, lack of health insurance, mental health disorders, use of illicit drugs, unstable housing, lower socioeconomic status, having other sexually transmitted infections, being a sex worker, more than 1 partner in the past year, and residence in an area of high prevalence.



* Per 100,000.
ACRONYMS: CS = Congenital syphilis; P&S = Primary and secondary syphilis.

Figure 2. Reported cases of congenital syphilis among 15-to 44-year-old female patients. From: Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. https://www.cdc.gov/std/stats18/toc.htm. (4)

(7)(8) There is a high prevalence of coinfection with human immunodeficiency virus (HIV) and syphilis, as syphilis increases the risk of HIV infection. (6) Maternal HIV and syphilis coinfection increases the risk of congenital syphilis; however, the mechanism of this increased transmission is not yet understood. (5)

Global Epidemiology

The World Health Organization (WHO) estimated that in 2016 there were 6 million new cases of syphilis globally and 1 million pregnant women had active syphilis infection. (1) The global congenital syphilis rate was 473 (range, 385–561)/100,000 live births with the rates being highest in the African and Eastern Mediterranean regions. (2) WHO estimated that there were 661,000 cases of congenital syphilis in 2016, related to 355,000 adverse birth outcomes, including approximately 204,000 stillbirths and neonatal deaths, 41,000 preterm or low-birthweight births, and 109,000 infants with clinical congenital syphilis. (2)

With 200,000 fetal and neonatal deaths each year attributable to syphilis, this infection is the second leading cause of preventable stillbirth globally, surpassed only by malaria. (3) WHO has a global health initiative to eliminate mother-to-child transmission of syphilis. The 661,000 global cases of congenital syphilis in 2016 were decreased from 750,000 total cases in 2012. (2) Twelve countries have eliminated mother-to-child transmission of syphilis and HIV. (3)

PATHOGENESIS

Syphilis was recognized as early as the end of the 15th century, with an awareness of the sexual mode of transmission by the 18th century; the causative agent was discovered in 1905. (5) It is caused by the bacterium *Treponema pallidum* subspecies *pallidum*. The bacteria are thin, corkscrew-shaped, flagellated, motile, gram-negative spirochetes. Humans are the only natural host. *T pallidium* has difficulty surviving outside the host and therefore, has not been able to be successfully grown in artificial media.

ACQUIRED SYPHILIS

An understanding of acquired maternal syphilis is crucial to the understanding of perinatal syphilis and its transmission. Acquired syphilis is primarily transmitted through sexual contact with an infected person, as the spirochete enters the body through broken or intact skin. It is estimated that there is a 30% chance of infection resulting from sexual contact with an infected person. (5) Acquired syphilis is divided into 4 stages: primary syphilis, secondary syphilis, latent syphilis (including early latent and late latent), and tertiary syphilis (Table 1).

Primary Syphilis

In acquired syphilis, following inoculation with spirochete the individual develops spirochetemia and eventually 1 or more

Table 1. Signs and Symptoms of Stages of Acquired Syphilis

Stage of Syphilis	Signs and Symptoms
Primary	Nontender, firm ulcer(s) (chancres) with adjacent localized painless lymphadenopathy
Secondary	Fever, sore throat, malaise, headache, myalgias/arthralgias, splenomegaly, generalized lymphadenopathy, macular papular rash (may involve palms and soles), condyloma lata, mucocutaneous lesions, alopecia
Latent	Asymptomatic but serology positive for syphilis infection
Tertiary	Destructive lesions (gummas) in various organs, bones, skin; aortitis
Neurosyphilis	Can occur at any stage of infection Meningitis, uveitis, seizures, optic atrophy, high stepping gait with foot slapping caused by posterior spinal cord degeneration with loss of proprioception (tabes dorsalis)

Content from Dobson and Sánchez (5) and American Academy of Pediatrics. (9)

painless indurated ulcers, called chancres, at the site of inoculation on average 3 to 4 weeks (range 10–90 days) after exposure. (5)(9) The chancre is an inflammatory reaction to the infection and may be accompanied by surrounding nontender lymphadenopathy. The chancre(s) usually heals within a few weeks.

Secondary Syphilis

The secondary stage occurs 1 to 2 months after onset of the primary chancre and is characterized by nonspecific systemic symptoms including fever, sore throat, myalgias, generalized lymphadenopathy, and a maculopapular rash that characteristically involves the palms and soles. (5)(9) Other symptoms may include splenomegaly, headache, arthralgias, malaise, alopecia, condyloma lata (hypertrophic papular lesions), and mucocutaneous lesions. (5)(9) The secondary stage spontaneously resolves in 3 to 12 weeks and the individual becomes asymptomatic and enters the latent stage. However, during this time secondary stage symptoms may intermittently flare up.

Latent Syphilis

The latent phase is a period in which the individual remains asymptomatic, but serologic findings are positive for syphilis infection. If the primary infection occurred within 1 year, it is called the early latent phase and if it is over 1 year, it is the late latent phase. Individuals are most infectious in the first year after acquiring syphilis. (5)

Tertiary Syphilis

Tertiary syphilis may occur 15 to 30 years after the primary infection. (9) It is characterized by the development of potentially destructive lesions, called gummas, in various organs, bones, or skin, or cardiac inflammation leading to aortitis.

Neurosyphilis

Involvement of the central nervous system (CNS), which results in meningitis, seizures, and ophthalmic involvement, may occur at any stage. Dementia and tabes dorsalis (degeneration of the dorsal columns of the spinal cord with loss of proprioception leading to high stepping gait, ataxia, and shooting pains) are late findings. (5)(9)

Pregnancy does not alter the course of syphilis in the female patient, though the fetus is at risk of acquiring syphilis, which may result in spontaneous abortion, stillbirth, perinatal death, hydrops fetalis, preterm birth, low birthweight, and congenital syphilis. (5)(9)(10)(11)

CONGENITAL SYPHILIS

The most common route of transmission to the fetus is transplacental—related to maternal spirochetemia, in which spirochetes pass from the pregnant woman's bloodstream directly into the fetal bloodstream. More rarely, the neonate can be exposed at the time of delivery through contact with infectious genital lesions. Transplacental transmission can occur throughout pregnancy but the risk is higher later in pregnancy. (10)(11) Transmission from the pregnant woman to the fetus can also occur in any stage of maternal syphilis, though the risk is highest in the primary and secondary stages, and with shorter length of time from the initial infection. (5)(10)(11)

Following fetal infection, there is hematogenous spread of the infection to nearly all fetal organs, with the most commonly affected being liver, pancreas, intestine, kidney, spleen, and bone. Because the spirochete is inoculated directly into the fetal bloodstream, the first stage of infection involving a chancre and lymphadenopathy is not present. (10) The effects on the fetus are from the resultant inflammatory response.

In utero transmission can result in abortion, stillbirth, and perinatal death; these occur in 40% of pregnancies with untreated early syphilis. (6) It can also result in hydrops fetalis, preterm birth, low birthweight, and symptomatic congenital syphilis; however, most infants are asymptomatic at birth. (8) Initially, asymptomatic infants, if untreated, may develop symptoms within 1 to 2 months of birth and others may not develop symptoms for years.

Clinical Presentation

Congenital syphilis is arbitrarily divided into early congenital syphilis, with manifestations before 2 years of age, and late congenital syphilis, with manifestations after 2 years of age (Table 2). The late manifestations can generally be prevented with treatment of the woman during pregnancy or treatment of the infant within the first 3 months of age; however, there are case reports of late manifestations despite adequate treatment. (5) Infants who are not treated, even if they were asymptomatic at birth, are at increased risk of developing late manifestations. (12)

Signs and Symptoms of Early Congenital Syphilis

By definition, early congenital syphilis leads to symptoms before 2 years of age, however manifestations generally present by 3 months of age and usually within the first 5 weeks after birth. (5) These manifestations are a result of the inflammatory reaction to infection. (10) The manifestations are diverse, potentially involving nearly every organ system, and varied in severity, with 1 or multiple organ systems affected. More common signs and symptoms include hepatomegaly and bony abnormalities; other signs

Table 2. Signs and Symptoms of Early and Late Congenital Syphilis

Congenital Syphilis	Signs and Symptoms
Early congenital syphilis	Liver/spleen: Hepatomegaly (with or without splenomegaly), elevated liver function tests, cholestasis, extramedullary hematopoiesis Bony abnormalities: Osteochondritis, periostitis, moth-eaten appearance of upper medial tibial metaphysis because of bone destruction (Wimberger sign), serrated metaphysis (Wegner sign), pseudoparalysis caused by pain, fracture, or dislocation (pseudoparalysis of Parrot) Dermatologic: Rhinitis (snuffles), maculopapular rash involving palms and soles, bullous rash (pemphigous syphiliticus), condyloma lata, fissures around mouth/anus, generalized lymphadenopathy (especially epitrochlear), edema Hematologic: Nonimmune hydrops, Coombs-negative hemolytic anemia, leukocytosis or leukopenia, thrombocytopenia, petechiae, purpura Lungs: Pneumonia, chest radiograph with bilateral opacification (pneumonia alba) and/or diffuse fluffy infiltrate Ophthalmologic: Chorioretinitis, iritis, cataracts, glaucoma Nonspecific: Low birthweight, intrauterine growth restriction, prematurity, failure to thrive Central nervous system: Meningitis, bulging fontanelle, seizures, cranial nerve palsies, cerebrospinal fluid abnormities, pituitary dysfunction with hypoglycemia and diabetes insipidus Less common: Diarrhea, necrotizing enterocolitis, pancreatitis, myocarditis, nephrotic syndrome
Late congenital syphilis	Ophthalmologic: Interstitial keratitis, uveitis, blindness Central nervous system: Hydrocephalus, seizures, intellectual disability, optic nerve atrophy, deafness, paralysis Skeletal: Anterior bowing of shin (saber shins), frontal bossing, sternoclavicular thickening (Higoumenakis sign), symmetric painless knee swelling (Clutton joints) Dental: Small, widely spaced, notched central incisors (Hutchinson teeth), extra cusps on lower molars (mulberry molars) Dermatologic: Saddle nose, perforation of hard palate, perioral scarring (rhagades)

Content from Dobson and Sánchez, (5) American Academy of Pediatrics, (9) Michaels et al, (10) and Esper. (11)

include rhinitis, rashes and mucocutaneous lesions, and hematologic manifestations, as well as ophthalmologic findings. (5)(9)(10)(11)

Hepatomegaly is the most common clinical manifestation. (5)(10) It may be present with or without splenomegaly, but isolated splenomegaly has not been described (differentiating it from other congenital infections, such as TORCH infections). The organomegaly is thought to be due to extramedullary hematopoiesis and hepatitis. (10) Hepatomegaly may be accompanied by elevated liver function tests and cholestasis; these may initially worsen with treatment, and then slowly resolve.

Bony abnormalities seen on radiography are another common sign and may be found in infants who are otherwise asymptomatic. (5)(10) They most commonly involve the long bones, especially of the lower extremities, and are usually symmetric. Abnormalities include osteochondritis, periostitis, the Wimberger sign (moth-eaten appearance of upper medial tibial metaphysis caused by bony destruction), and the Wegner sign (serrated metaphysis). These findings may be noted at birth or within the first few weeks and typically heal by 6 months with or without treatment. Bony changes can rarely cause clinical pseudoparalysis due to pain, fracture, or dislocation (pseudoparalysis of Parrot). Because bony radiographic abnormalities may be found in otherwise asymptomatic infants and may be present at birth or shortly after birth, radiography of long bones can be helpful in evaluating the presence of congenital syphilis (see "Diagnosis").

Other findings include syphilitic rhinitis (snuffles), which typically occurs in the first week after birth. A rash may present 1 to 2 weeks after the snuffles. This rash is typically maculopapular, involves the palms and soles, progresses to a copper color, and then desquamates. However, a disseminated bullous rash may be present at birth (pemphigous syphiliticus) and other dermatologic findings may be seen such as condyloma lata and fissures around the mouth and anus. Lymphadenopathy may occur, especially epitrochlear lymphadenopathy (which is relatively specific for syphilis). (10)

Hematologic abnormalities include hydrops, hemolytic anemia (Coombs negative), low or high white blood cell count, and thrombocytopenia potentially leading to petechiae and/or purpura. (11)

Chest radiography has historically shown bilateral opacification (pneumonia alba); however, a diffuse fluffy infiltrate is now more commonly seen with increasing use of penicillin. (5)

Ophthalmologic findings include chorioretinitis, iritis, cataracts. and glaucoma. (10)

Other less common findings include edema, diarrhea or necrotizing enterocolitis due to gastrointestinal tract inflammation, pancreatitis, myocarditis, and nephrotic syndrome. (10) Nonspecific symptoms include low birthweight, intrauterine growth restriction, and failure to thrive. (11)

CNS involvement may include meningitis, bulging fontanelle, seizures, and cranial nerve palsies. Since the introduction of penicillin, it has become unusual for infants to have early CNS symptoms but they may develop later if the infant is not treated. (5) Therefore, CNS infection is typically diagnosed based on cerebrospinal fluid (CSF) abnormalities (though this is not straightforward, see "Diagnosis"). Asymptomatic CNS infection may be present in 40% of infants who have other findings of syphilis on examination, laboratory abnormalities, or radiography. (13)

Signs and Symptoms of Late Congenital Syphilis

By definition, in late congenital syphilis, symptoms present after 2 years of age, but they often occur much later than that, such as in childhood or adulthood. The manifestations of late congenital syphilis are the result of persistent inflammation and scarring. (10) Some manifestations, but not all, can be prevented with treatment during pregnancy or within the first 3 months of age. Keratitis and saber shins (anterior bowing of the tibia caused by periostitis) may occur or progress despite early treatment. (5) Clinical manifestations include ophthalmologic, CNS, skeletal, dental, and dermatologic changes. (5)(9)(10)(11)

Ophthalmologic. The most common late manifestation is interstitial keratitis which can progress to blindness. It typically occurs around puberty but can occur between 4 and 30 years of age. (5) Uveitis may also develop.

Central Nervous System. Various CNS manifestations can occur including deafness, hydrocephalus, seizures, intellectual disability, optic nerve atrophy, and paralysis.

Skeletal. Some late skeletal manifestations result from early periostitis, including anterior bowing of shins (saber shins, from periotitis of tibia), frontal bossing (from periostitis of the forehead), and sternoclavicular thickening (Higoumenakis sign, from periostitis of the clavicle). Other skeletal manifestations include symmetric painless knee swelling (Clutton joints). (10)

Dental. Manifestations include small, widely spaced, notched central incisors (Hutchinson teeth) and lower molars with extra cusps (mulberry molars).

Dermatologic. Early syphilitic rhinitis may result in a saddle nose and rarely, perforation of the hard palate (relatively specific for syphilis). (10) Early fissures can result in perioral scarring (rhagades).

Interstitial keratitis, deafness due to eighth cranial nerve, and Hutchinson teeth make up the Hutchinson triad which is rather specific for congenital syphilis. (11)

DIAGNOSIS

Screening of Pregnant Women

Prevention of congenital syphilis depends on screening and identifying pregnant women with syphilis and providing adequate treatment. The United States Preventive Services Task Force and Centers for Disease Control and Prevention (CDC) recommend that pregnant women should be screened for syphilis early in pregnancy. (12)(14) The CDC and joint guidelines from the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists recommend screening be repeated at 28 to 32 weeks of gestation and at the time of delivery for high-risk individuals (ie, no evidence of prior testing, uninsured or low income, having unprotected sex with >1 partner, diagnosed with sexually transmitted infection during pregnancy, illicit drug use, receiving money in exchange for sex or drugs) and in high-prevalence communities. (12)(15)(16) This is because false negatives are possible in early infection and infection can be acquired throughout pregnancy.

Serologic screening consists of nontreponemal and treponemal tests. The nontreponemal tests include the VDRL and rapid plasma reagin (RPR) tests. These tests are generally inexpensive, rapid, and quantifiable, which allows for monitoring of disease and response to therapy. As is characteristic of most screening tests, they are more sensitive than specific. These tests detect IgG and IgM antibodies to cardiolipin released from infected host cells. (16) False-negative results can occur in the very early and late stages of disease and as a result of the prozone phenomenon (ie, when very high antibody titers exceed the

zone of detection). (17) False-positive results can also occur because of pregnancy, viral infections, tuberculosis, lymphoma, connective tissue disease, and intravenous drug use, among other things. Therefore, a positive result on a nontreponemal test must be confirmed with a treponemal test. (9)

The treponemal tests include *T pallidum* particle agglutination, *T pallidum* enzyme immunoassay, *T pallidum* chemiluminescent assay, and fluorescent treponemal antibody absorption. These detect IgG and IgM antibodies specific to *T pallidum*. (16) The treponemal tests are also not perfect and false-positive results can occur, typically because of other spirochete diseases such as Lyme disease. (5)

Nontreponemal titers usually decrease 4-fold within 6 to 12 months of adequate treatment, and become nonreactive by 1 year, especially if treatment was initiated in the primary or secondary stage. (5)(9) However, some individuals may have ongoing low nontreponemal titers, especially if initial treatment occurred in a later stage of disease. A 4-fold decrease in nontreponemal titers indicates adequate treatment, whereas a 4-fold increase in titers indicates relapse or reinfection. (9) In contrast, treponemal tests typically, but not always, remain reactive for life even after treatment. (9)

The "conventional screening" method, which is recommended by the CDC and United States Preventive Services Task Force, includes screening first with a nontreponemal test and performing confirmatory testing with a treponemal test. (12)(14) The "reverse screening" method (which is increasingly being used because it can be automated and therefore, has faster turnaround times and lower costs) starts with a treponemal test followed by a nontreponemal test. (9)

In the conventional screening program, a positive nontreponemal test followed by a positive treponemal test is diagnostic of syphilis. A positive nontreponemal test followed by a negative treponemal test may be a false-positive nontreponemal test or be consistent with early syphilis. (12) Retesting in 2 to 4 weeks should be considered. A negative nontreponemal test does not need confirmatory testing.

In the reverse screening program, a positive treponemal test followed by a positive nontreponemal test is diagnostic for past or current syphilis. A positive treponemal test followed by a negative nontreponmeal test, should lead to a repeat treponemal test with a different test. If the repeat is positive, it may be because of adequately treated prior syphilis or untreated late-stage syphilis. If the repeat treponemal test is negative, the initial positive result may have been a false-positive result. (9) The reverse screening program may be better than the conventional screening program at detecting latent and tertiary syphilis. (18)

If syphilis is diagnosed during pregnancy, the woman should also be tested for HIV and other sexually transmitted infections. (12) If syphilis is diagnosed in the second half of pregnancy, fetal ultrasonography should be performed after 20 weeks' gestation, because the fetal immune system is immature and no ultrasound findings are typically seen before that. (16) Ultrasonography should assess for signs of fetal syphilis including hepatomegaly, elevated middle cerebral artery peak systolic velocity (indicating fetal anemia), placentomegaly, polyhydramnios, ascites, and hydrops. (16) These signs may also indicate inadequate fetal treatment. If stillbirth occurs after 20 weeks' gestation, the woman should be tested for syphilis. (9)

Diagnosis in the Neonate

Syphilis can be definitively diagnosed with visualization of spirochetes on microscopic darkfield examination or on silver staining or direct fluorescent antibody staining for *T pallidum* of lesions, fluids (nasal discharge), or pathology tissue (placenta, umbilical cord). (5) Placental and umbilical cord pathology may give clues to the diagnosis. In congenital syphilis, the placenta is typically large, thick, and pale (19) and the umbilical cord is edematous, with red and blue stripes and chalky discoloration (barber's pole) and may have necrotizing funisitis. (19) Testing of the lesion or fluid with polymerase chain reaction (PCR) can also be used to make the diagnosis but is not widely available.

Definitive diagnosis of congenital syphilis is often difficult and in practice, a presumptive diagnosis is typically made with serologic testing. The CDC recommends that prior to a newborn being discharged from the hospital, the results of the mother's serologic status for syphilis during pregnancy be reviewed. If a mother was at high risk, her serologic status should be tested again at the time of delivery. (12) If the mother's serologic test result is truly positive, the infant needs the same nontreponemal test performed on the mother and a thorough newborn examination. The same nontreponemal test should be performed so it can quantitatively be compared with the mother's nontreponemal test result. The sample should be drawn from serum, not cord blood, as cord blood may be contaminated by maternal blood or Wharton jelly. (12) The diagnosis of congenital syphilis in the neonate is complicated because maternal nontreponemal and treponemal IgG

antibodies can be transferred across the placenta during gestation. (5)(9) Therefore, the antibody detected in the neonate may be maternal in origin. However, it is unlikely that the nontreponemal antibody titers of the neonate would be 4-fold greater than the mother's simply because of transmission, so a 4-fold greater titer is consistent with highly probable congenital syphilis. (12) A neonatal nontreponemal titer that is less than 4-fold greater than the mother's titer does not exclude a diagnosis of congenital syphilis. (9)

The AAP has published an algorithm for assessment of maternal serology and recommended neonatal evaluation and management that can help guide clinical care (Fig 3). (9)

The infant's evaluation and treatment depend on the mother's treatment history for syphilis:

- If maternal treatment was inadequate (none, undocumented, ≤4 weeks before delivery, nonpenicillin drug, 4-fold or greater increase in titers indicating reinfection/relapse, partner recently diagnosed) the infant needs to have the same nontreponemal test as the mother, a thorough examination, and a complete evaluation.
    - If the physical examination findings are abnormal, OR the evaluation result is abnormal or incomplete, OR the RPR/VDRL is 4-fold or greater than the maternal RPR/VDRL, this is considered "proven or highly probable congenital syphilis" and requires treatment according to the recommendations for the "proven or highly probable congenital syphilis" category (Table 3).
    - If the physical examination findings are normal, AND the evaluation result is normal, AND the RPR/VDRL is less than 4-fold that of the maternal RPR/VDRL this is considered "possible congenital syphilis" and requires treatment according to the recommendations for "possible congenital syphilis" (Table 3).

- If maternal treatment was during pregnancy and adequate (penicillin, >4 weeks before delivery, and no evidence of reinfection/relapse) the evaluation depends on the infant's nontreponemal test and physical examination findings:
    - If either the infant's nontrepnemal titers are 4-fold greater than the maternal titers OR the infant's physical examination findings are abnormal this is considered "proven or highly probable congenital syphilis" and the infant needs a full evaluation and treatment according to the "proven or highly probable congenital syphilis" treatment guidelines (Table 3).
    - If the nontreponemal titers are the same as or less than 4-fold the maternal titer AND the physical examination findings are normal, this is categorized as "congenital syphilis less likely" and the infant needs no further immediate evaluation but does require treatment according to recommendations for "congenital syphilis less likely" category (Table 3).

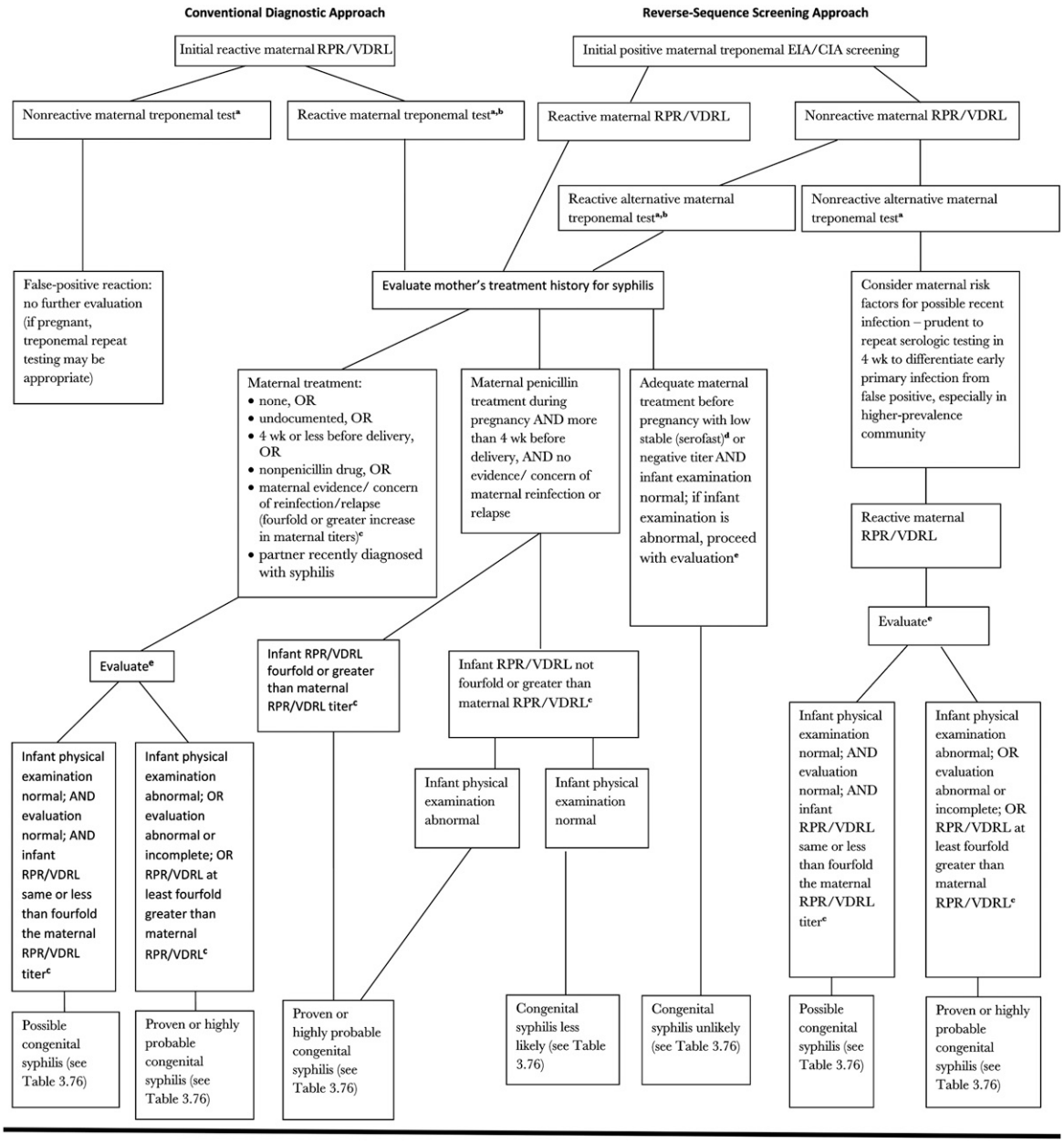
- If the mother had adequate treatment *before* pregnancy *with stable low titers* AND the infant's examination findings are normal, this is categorized as "congenital syphilis unlikely" and the infant needs no further immediate evaluation or treatment. However, neonates should be followed and retested, and some experts recommend considering treatment if follow-up is uncertain (see "congenital syphilis unlikely" in Table 3).

- A full evaluation consists of a complete blood cell count, CSF examination for cell count, protein, and glucose, and quantitative VDRL, and as clinically indicated long bone radiography, liver function tests, ophthalmologic examination, chest radiography, head ultrasonography, and auditory brainstem response.

Syphilis of the CNS/Congenital Neurosyphilis

Syphilis of the CNS is a difficult diagnosis to establish in neonates. It is typically inferred from CSF testing following lumbar puncture, with white blood cell counts greater than 25/μL (0.025×10^9/L), protein concentration greater than 0.15 g/dL (1.5 g/L) if less than 1 month old (>0.17 g/dL [1.7 g/L] if preterm), or positive VDRL being consistent with congenital neurosyphilis; these definitions are by convention, with some centers using varying values. (5)(10) None of these markers is highly sensitive or specific. (13) In fact, though VDRL of the CSF should be performed and may be helpful, false-positive results (caused by maternal IgG levels that cross the placenta and may appear in the infant's CSF as well as a bloody spinal tap) and false-negative results may also occur. (5)(10) PCR may help but is not widely available in the clinical setting.

Because asymptomatic CNS infection may be present in 40% of infants who have other findings of syphilis, neurosyphilis is presumed if clinical, radiographic, or laboratory abnormalities are compatible with a diagnosis of syphilis to prevent long-term morbidity. (13) This does not change treatment (see "Management") but affects follow-



RPR indicates rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

[a] *Treponema pallidum* particle agglutination (TP-PA) (which is the preferred treponemal test), fluorescent treponemal antibody absorption (FTA-ABS), or microhemagglutination test for antibodies to *T pallidum* (MHA-TP).

[b] Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment for syphilis.

[c] A fourfold change in titer is the same as a change of 2 dilutions. For example, a titer of 1:64 is fourfold greater than a titer of 1:16, and a titer of 1:4 is fourfold lower than a titer of 1:16. When comparing titers, the same type of nontreponemal test should be used (eg, if the initial test was an RPR, the follow-up test should also be an RPR).

[d] Stable VDRL titers 1:2 or less or RPR 1:4 or less beyond 1 year after successful treatment are considered low serofast.

[e] Complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (eg, chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response).

Figure 3. Approach to infants born to mothers with reactive serologic test for syphilis. From: American Academy of Pediatrics. Syphilis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* Itasca, IL: American Academy of Pediatrics; 2018;773–788. (9)

Table 3. Treatment Recommendations for Congenital Syphilis for Infants <1 Month of Age by Likelihood Category of Congenital Syphilis

Category	Treatment
Proven or highly probable congenital syphilis	• Aqueous crystalline penicillin G, 50,000 U/kg, IV, every 12 h (≤1 week), then every 8 h for infants >1 week, for a total of 10 days of therapy (*preferred*) OR • Procaine penicillin G, 50,000 U/kg, IM, as a single daily dose for 10 d
Possible congenital syphilis	• Aqueous crystalline penicillin G, 50,000 U/kg, IV, every 12 hours (≤1 week), then every 8 h for infants >1 week, for a total of 10 d of therapy (*preferred*) OR • Procaine penicillin G, 50,000 U/kg, IM, as a single daily dose for 10 d OR • Benzathine penicillin G, 50,000 U/kg, IM, single dose (only if evaluation is complete, including CSF, and normal, and follow-up is certain)
Congenital syphilis less likely	• Benzathine penicillin G, 50,000 U/kg, IM, single dose (*preferred*) • Alternatively, if the mother's nontreponemal titers decreased at least 4-fold after appropriate therapy for early syphilis or remained stable at low titers, the infant may not be treated but followed every 2–3 months until the nontreponemal test becomes nonreactive • Nontreponemal antibody titers should decrease by age 3 mo and be nonreactive by age 6 mo, if titers are stable or increasing at age 6–12 mo, the infant should undergo a complete evaluation and 10-day course of treatment, even if previously treated
Congenital syphilis unlikely	• No treatment • However, neonates with negative nontreponemal tests at birth whose mother was seroreactive at delivery should be retested at 3 mo to rule out incubating syphilis at the time of birth • An infant with reactive nontreponemal tests should be followed to ensure results turn negative • Some experts recommend considering treatment of infants with a reactive test and uncertain follow-up with a single dose of benzathine penicillin G 50,000 U/kg, IM, single dose

Content from American Academy of Pediatrics (9) and Workowski et al. (12)

up. Overall, treatment with penicillin is relatively benign compared with missed treatment.

MANAGEMENT

Intravenous or intramuscular penicillin G is the mainstay of treatment for syphilis during pregnancy and for congenital syphilis or congenital neurosyphilis, as it is the only therapy that has evidence to support its use in these settings. (9) It has proven efficacy and minimal toxicity. (20)(21) *T pallidum* remains extremely sensitive to penicillin. (5)

In pregnant women, dosing and interval of administration is based on the stage of syphilitic disease. The CDC has published treatment guidelines. (12) If the pregnant woman has a history of penicillin allergy, she should undergo skin testing, and if there is concern for severe allergy, penicillin desensitization followed by treatment with penicillin remains the standard of care. Risk factors for treatment failure include higher titers and unknown length of infection. (12)

Maternal treatment is very effective at preventing congenital syphilis, with an estimated efficacy of 98% in women who deliver after 20 weeks' gestation. (20) On the other hand, untreated pregnant women have an 80% chance of passing syphilis to their infant according to the CDC, and abortion, stillbirth, and perinatal death occur in 40% of pregnancies with untreated early syphilis. (6)(20)(22)(23)

In neonates, dosing is based on risk of having congenital syphilis determined with infant nontreponemal testing, physical examination, maternal history of treatment, and in some cases evaluation (as noted before). The AAP has published treatment guidelines (based on CDC treatment guidelines) which should guide clinical care (Table 3). (9) For infants who have "proven or highly probable congeni-

tal syphilis" or "possible congenital syphilis" (ie, those with abnormal physical examination findings consistent with syphilis, or 4-fold higher nontreponemal titers compared with maternal titers, or pathologic findings positive for syphilis [darkfield microscopy, positive treponemal-specific antibody result, positive PCR], or inadequate maternal treatment, or any abnormal findings on evaluation [including laboratory tests, CSF studies, radiography]), intravenous penicillin G for 10 days is recommended. Dosing is based on chronologic age and requires adjustment if it is started within the first week after birth. Penicillin G at 50,000 U/kg is given every 12 hours through 7 days of age, followed by 50,000 U/kg every 8 hours starting at 8 days of age. Penicillin dosing also changes after 1 month of age. If treatment is missed for 1 day, the entire 10-day course must be repeated. Other antibiotics (such as ampicillin to rule out sepsis) should not count toward the 10-day course of penicillin. The levels of penicillin in CSF are higher with intravenous aqueous crystalline penicillin G than intramuscular procaine penicillin G but the clinical significance of this is unknown. (24) For situations of penicillin shortage, the CDC has published recommendations for each of the different clinical scenarios including whether alternative treatment, such as with ceftriaxone, can be considered. (12)

The possibility of a Jarisch-Herxheimer reaction occurring after the start of treatment has been described and attributed to rapid killing of spirochetes and endotoxin release. It typically presents in the first 24 hours of treatment with systemic symptoms and may include fever, headache, tachypnea, tachycardia, and sometimes hypotension. (5)(10) In pregnant women, this reaction may contribute to preterm labor and fetal decelerations; however, this would not be a reason to delay treatment—some specialists recommend giving the first dose on the labor and delivery floor with continuous fetal monitoring for at least 24 hours. (16) The Jarisch-Herxheimer reaction is relatively rare in the neonate. (5)

FOLLOW-UP AND PROGNOSIS

All infants born to a mother who tests positive for syphilis at delivery (whether the infant's serology was positive or not) should have careful follow-up at regularly scheduled health maintenance visits at 1 month (if not treated) and 2, 4, 6, 12, 15, and 24 months, with a nontreponemal test every 2 to 3 months (until it becomes nonreactive). (9) If there is concern for neurosyphilis, a lumbar puncture with CSF evaluation every 6 months (until the CSF studies have normalized) is recommended. (9)(12) Even if the neonate's serology was nonreactive at birth, testing should be repeated at 3 months to ensure it was not very early incubating syphilis. (9)

Regardless of whether the infant's nontreponemal titers were reactive because of true infection (and the infant was subsequently adequately treated) or because of maternal antibody transfer, nontreponemal titers should decrease by 3 months of age and become nonreactive by 6 months of age. (5)(9) If titers are stable or increasing at 6 to 12 months after treatment, infants should be reevaluated and treated. (9) Similarly, if CSF VDRL is still positive at 6 months of age, the infant should be reevaluated and re-treated. (9) Neuroimaging should also be considered.

Maternal antibodies can last until 15 months of age, so a reactive treponemal test at 18 months of age (when maternal antibodies are gone) confirms the diagnosis of congenital syphilis. (5) A corresponding negative nontreponemal test indicates no current infection. In addition, neurologic, hearing, and ophthalmologic examinations should be performed annually and development should be closely followed throughout childhood. (9) Data on long-term outcomes for these infants are lacking. (5)

PREVENTION

The best way to treat congenital syphilis is to prevent it in the first place. This requires commitment and resources to provide adequate prenatal care for women, including early and repeat syphilis testing during pregnancy, diagnosis, appropriate treatment including treatment of partners, and effective follow-up, as well as diagnosis and treatment of women and their partners before pregnancy. It also requires complete assessment of neonates at risk and treatment when appropriate.

In developing countries, point-of-care combined syphilis/HIV tests (which are relatively low cost, rapid, and as accurate as serologic testing) are increasingly being used. (2) This could help decrease the global burden of syphilis.

Adequate contact precautions should also be used because lesions, fluids (rhinitis), and potentially blood may have significant levels of infectious spirochete. Transmission does not occur through breast milk, unless there is a chancre on the breast. (5) In addition, syphilis is a reportable disease and diagnoses should be reported to the local public health department. (25) This is important as it helps with contact tracing and treatment of other individuals who are at risk. The local public health department is also an excellent resource for obtaining information about maternal treatment.

Summary

Maternal-to-fetal transmission of syphilis results in spontaneous abortion, stillbirth, perinatal death, congenital syphilis, and long-term physical and neurologic problems. In the United States, the number of congenital syphilis cases increased 291% from 2012 to 2018. (4) Given our medical knowledge of the disease and existence of inexpensive and effective treatment, congenital syphilis should be nearly preventable with adequate testing and treatment of pregnant women and their partners. A 2018 CDC analysis of missed prevention opportunities found that nationally, a lack of adequate maternal treatment despite timely diagnosis of syphilis during pregnancy (30.7%) and lack of timely prenatal care (28.2%) were the most common problems (though there was some variation by region). (8) It is time to redouble our public health efforts to stop the increase of this relatively preventable congenital disease and its associated morbidities and mortalities.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal infections with *Treponema pallidum*.
- Know the clinical manifestations and diagnostic features of perinatal infections with *T pallidum*.
- Know the management and complications of perinatal infections with *T pallidum*.
- Know the rationale, methods, and interpretation of results of screening for maternal infections such as rubella, CMV, viral hepatitis, HIV, and syphilis.
- Know the cutaneous manifestations of congenital syphilis.

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NEO QUIZ

1. Syphilis in the general population and congenital syphilis has been increasing in some regions in recent years. Which of the following is noted to be a significant adverse consequence of syphilis infection?

   A. Stillbirth.
   B. Milk protein allergy.
   C. Acute lymphocytic leukemia.
   D. Renal vein thrombosis.
   E. Hemolytic uremic syndrome.

2. Since 2012, the rates of congenital syphilis have increased in the United States. Which of the following statements regarding risk for congenital syphilis is true?

   A. The main reason for this observed increase was a definition change that occurred in 2010.
   B. The highest increases regionally have been in the northern and eastern states.
   C. In recent years, the highest incidence by race is in infants born to Asian mothers.
   D. Risk factors include mental health disorders, use of illicit drugs, and unstable housing for the mother.
   E. Maternal human immunodeficiency virus infection appears to be protective for syphilis acquisition and transmission of syphilis.

3. A county public health officer notes that the prevalence of syphilis in the community is increasing, with a corresponding increase noted in cases of congenital syphilis. The plans are to increase screening to prevent progression of disease and to prevent congenital syphilis. Which of the following statements regarding congenital syphilis is correct?

   A. Transmission via exposure contact at the time of delivery is more likely to cause disease than transplacental transmission.
   B. Transplacental transmission is more common in the earlier portion of pregnancy compared to the later part of pregnancy.
   C. Transmission risk is highest in the primary and secondary stages of syphilis, and with shorter length of time from initial infection.
   D. Perinatal death occurs in virtually 100% of pregnancies with untreated syphilis.
   E. Most infants with congenital syphilis have symptoms of critical illness within 1 to 2 hours after birth.

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4. An infant is noted to have hepatomegaly and a history of untreated syphilis in the mother. Which of the following statements best characterizes the presentation of early congenital syphilis?

    A. Aside from hepatomegaly, a sole finding of isolated splenomegaly is the most common manifestation.
    B. Hepatomegaly is almost always associated with normal liver function tests including normal bilirubin, distinguishing from other liver disease.
    C. Bony abnormalities may be seen in infants who are otherwise asymptomatic and most commonly involve the long bones, especially of the lower extremities, and are usually symmetric.
    D. Syphilitic rhinitis usually does not present until after 4 weeks of age and is typically accompanied by mucous discharge from the eyes.
    E. When a rash is present, it is typically vesicular and spares the palms and soles.

5. Several key strategies are used to prevent congenital syphilis. Which of the following statements characterizes current recommendations regarding screening correctly?

    A. Pregnant women can receive verbal screening for syphilis based on sexual history, with laboratory testing performed based on risk factors obtained from the history.
    B. In high-prevalence areas, laboratory screening of all infants is recommended.
    C. The rapid plasma reagin test is highly sensitive, therefore, false positives are exceedingly rare.
    D. In the conventional screening program, a positive nontreponemal test result followed by a negative treponemal test result may be a false-positive nontreponemal test or early syphilis, and retesting in 2 to 4 weeks should be considered.
    E. In the reverse screening program, a negative nontreponemal test result followed by a negative treponemal test result should be followed by repeating both tests in 1 month.