**Prevention and treatment of mother-to-child transmission of syphilis**

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**CONFLICTS OF INTEREST**

None

**Abstract**

*Purpose of review:*

Athough more than 90% of syphilis cases are diagnosed in developing countries, syphilis rates in industrialised countries have been increasing since the 1980s. Untreated syphilis in pregnancy is associated with high rates of adverse pregnancy outcomes, including foetal loss, premature birth, congenital syphilis and neonatal death. We reviewed the recent literature on adverse pregnancy outcomes associated with untreated syphilis and the benefits of early and effective treatment.

*Recent findings:*

Up to two-thirds of pregnant women with untreated syphilis may develop unwanted complications compared to a barkground rate of 14% in pregnant women without syphilis. A review of interventions to screen and manage infections during pregnancy found that those focussing on syphilis demonstrated an 80% reduction in stillbirths as compared with strategies to treat, detect or prevent other infections in pregnancy, such as malaria (22% reduction), HIV (7% reduction) or bacterial vaginosis (12% reduction). Detection and treatment of syphilis before the third trimester (28 weeks) can revert the risk of adverse outcomes to background rates.

*Summary:*

Transplacental transmission of syphilis, especially in the third trimester, is associated with high rates of adverse outcomes, but the risk can be significantly reduced with early detection and treatment in the first and second trimester, along with careful management of the infant after birth.

*Keywords (3-5):*

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| --- | --- |
| Pregnancy outcome | Syphilis, Congenital |
| Prenatal care | Child health |
| Prenatal diagnosis |  |

**Introduction**

Syphilis is a sexually transmitted disease and, if left untreated, is associated with a high case fatality rate of up to 60% and serious long-term complications among survivors. Syphilis has been called the “great imitator” because it has so many symptoms which can often mimic other infectious and non-infectious diseases (**Table 1**). During the 18th and 19th centuries, syphilis was very common in Europe, but declined rapidly with widespread use of [antibiotics](http://en.wikipedia.org/wiki/Antibiotic) in the early 20th century. Most cases of syphilis are now diagnosed in low- and middle-income countries, where 90% of the estimated 12 million cases occur.1 In the UK and other industrialised countries, however, syphilis rates have been increasing in men and women since the 1980s, particularly among [intravenous drug users](http://en.wikipedia.org/wiki/Recreational_drug_use), HIV-infected individuals, and men who have sex with men.2 Increased rates among heterosexuals have also been reported since the 1990s, especially in Eastern Europe and Asia, and has been attributed to unsafe sexual practices, such as sexual promiscuity, prostitution, and decreasing use of barrier protection.

**Transmission**

Syphilis is caused by a spiral-shaped, highly mobile spirochaete, *Treponema pallidum*, which is transmitted by direct contact with a syphilis sore during vaginal, anal, or oral sex. The spirochaete is able to pass through intact mucous membranes (mouth, vagina, rectum) or compromised skin. Around 30-60% of those exposed to primary or secondary syphilis will get the disease; inoculation with only 57 organisms results in a 50% chance of being infected. Sores can be found on the penis, vagina, anus, rectum, lips and mouth. The infection can also be transmitted from mother to foetus during pregnancy or childbirth (congenital syphilis). Humans are the only known [natural reservoir](http://en.wikipedia.org/wiki/Natural_reservoir). It has a slow doubling time of >30 hours, which explains the chronic nature of the infection.

**Syphilis in pregnancy**

Syphi­lis in pregnancy is not rare. Globally, far more pregnant women have syphilis than human immunodeficiency virus (HIV) infection: 1.9 million (in 2008) and 1.5 million (2010), respectively, mostly in developing countries.1 The proportion of pregnant women with syphilis who are diagnosed and treated during pregnancy is unknown, but estimates suggest that it is less than 10%. The risk of transplacental infection of the fetus is 60-80%, and the likelihood of infection is increased during the second half of pregnancy. Mother-to-child transmission is higher in untreated maternal primary or secondary syphilis (60-90%), decreasing to 40% in early latent syphilis, and <10% in late latent syphilis. This compares with 20% mother-to-child *in utero* transmission rate for HIV. In [sub-Saharan Africa](http://en.wikipedia.org/wiki/Sub-Saharan_Africa), syphilis contributes to ~20% of [perinatal deaths](http://en.wikipedia.org/wiki/Perinatal_death). Two-thirds of syphilitic infants are asymptomatic at birth and the infection may remain clinically silent throughout their lifetime. In infants, manifestations of syphilis are classified as early congenital (birth to 2 years) and late congenital (after 2 years).

**Early congenital syphilis** commonly manifests during the first 3 months of life with [hepatosplenomegaly](http://en.wikipedia.org/wiki/Hepatosplenomegaly) (70%), rash (70%), fever (40%), neurosyphilis (20%), pneumonitis (20%) and generalised lymphadenopathy. The rash may manifest as vesicular, bullous or a macular copper-colored rash on the palms and soles with papules around the nose, mouth and diaper area, as well as petechial lesions. The infant may fail to thrive and have a characteristic muco-purulent or blood-stained nasal discharge causing snuffles. A few infants develop meningitis, with complications such as choroiditis, hydrocephalus or seizures, with consequent long-term neurodevelopmental sequelae. In the first year of life, damage to the long bones and ribs can cause characteristic radiological changes with limb pseudoparalysis.

**Late congenital syphilis** typically manifests after two years of life if the early congenital infection is not appropriately treated. Late congenital syphilis is characterised by gummatous ulcers on the nose, nasal septum, hard palate and around the bones, resulting in saber shins (sharp forward bowing of the tibia) and bossing of the frontal and parietal bones of the skull. Neurosyphilis is usually asymptomatic, but paresis and tabes dorsalis may develop in adolescence. Damage to the optic nerve can lead to recurrent interstitial keratitis (inflammation of the cornea), often resuling in permanent scarring, and blindness. Progressive sensorineural deafness may appear at any age and is irreversible. Infrequently, malformations of the teeth and jaw bones result in the characteristic “Hutchinson” incisors, “mulberry molars”, rhagades (fissures, cracks, or linear scars at the angles of the mouth and nose) and “bulldog” facies.

**Risk of adverse pregnancy outcomes**

Adverse pregnancy outcomes of syphilis include foetal loss or stillbirth and, in liveborn infants, premature birth, low birthweight, congenital syphilis or neonatal death. A recent systematic review identified 3,258 publications and included six large case-control studies which, together, showed that 66.5% of pregnant women with untreated syphilis had adverse pregnancy outcomes compared with 14.3% in pregnant women without syphilis.3 Foetal loss and stillbirth were 21% more frequent, neonatal deaths 9% and prematurity or low birthweight 6% more frequent than among women without syphilis. Additionally, 15% of infants had clinical evidence of congenital syphilis and there was a 10% higher risk of death compared to infants born to uninfected mothers. In a large Tanzanian study, 94% of stillbirths and 77% of any adverse pregnancy outcomes in women with untreated syphilis were attributed to the infection and, among live-births to women with untreated syphilis, the infection accounted for 70% of low birthweight and 84% of premature infants.4 Notably, women with untreated syphilis were six times more likely to deliver prematurely than uninfected pregnant women.

In 2008, it was estimated that around 521,000 adverse pregnancy outcomes were associated with maternal syphilis globally, including 212,000 stillbirths or early foetal deaths, 92,000 neonatal deaths, 65,000 preterm or low birthweight infants and 152,000 infected newborns.5 The high rate of adverse pregnancy outcomes is probably due to direct damage caused by *Treponema pallidum* to both the placenta (microvascular proliferation and inflammation) and the umbilical cord – both of which will compromise foetal growth and viability.

**Early detection and treatment in pregnancy**

Early detection and treatment of syphilis in pregnancy can significantly reduce adverse pregnancy outcomes, including stillbirths, perinatal deaths and congenital syphilis.6 An analysis of 25 published studies assessing effectiveness of interventions to screen and manage infections during pregnancy found that those focussing on syphilis showed a significant 80% reduction in stillbirths than strategies to treat, detect and/or prevent malaria (22% reduction) HIV (7% reduction) or bacterial vaginosis (12% reduction).7 In Tanzania, treatment of 133 pregnant women with active syphilis and high antibody titres (and, therefore, high risk of transplacental transmission) and 249 women with low-titre syphilis with a single dose of benzathine penicillin reduced adverse birth outcomes (stillbirth, low birthweight and premature births) to background rates, as assessed through follow-up of 950 uninfected women.8

In China, where 500,000 pregnant women were screened and 1,855 women were identified and treated for syphilis during 2002-2005, the rate of mother-to-child transmission was significantly reduced from 54/100,000 to 22/100,000.9 The authors noted that nearly all the reduction was observed in women who were treated before the third trimester (28 weeks); the infants of women who first sought antenatal care in the third trimester or at delivery had often already developed congenital syphilis.

**Timing of detection and treatment**

A recent systematic review identified 1,199 studies, selected 84 for further review and included five studies to assess the optimal timing of antenatal interventions to prevent mother-to-child transmission of syphilis and associated adverse outcomes.10 All the studies showed a lower prevalence of adverse outcomes among women who received an intervention (that included screening and treatment) in the first and second trimesters compared to the third trimester. Adverse outcomes were 2.2 times more common in women treated in the third trimester compared to treatment in the first or second trimester. There was also a 2.1-fold higher risk of prematurity in mothers presenting late to antenatal clinic.

**Investigations**

The diagnosis of syphilis can be confirmed by direct visual inspection using [microscopy](http://en.wikipedia.org/wiki/Microscopy) or by diagnostic blood tests (**Table 2**).11 These tests, however, cannot distinguish between different disease stages. In early congenital syphilis, the diagnosis is usually suspected because of maternal disease. At birth, the neonate should have a thorough clinical examination, with darkfield microscopy (where available) of the placenta, umbilical cord and any skin/mucosal lesions, as well as a quantitative nontreponemal serum test (RPR/VDRL); testing cord blood is less sensitive and less specific. Those with clinical disease or suggestive serological test results should have additional blood tests (full blood counts, liver function tests, inflammatory markers), lumbar puncture (cell count, VDRL, protein), long-bone x-rays, and other investigations as clinically indicated (ophthalmological review, hearing tests, x-rays, neuroimaging). Diagnosis can be confirmed by microscopic visualization of spirochetes. Neonatal serology is complicated by the presence of transplacentally-acquired maternal IgG antibodies. However, a neonatal nontreponemal antibody titre >4 times the maternal titre would support active infection because such a high ratio is unlikely to be achieved through passive transfer.

Since maternal disease acquired late in pregnancy may be transmitted before development of antibodies, syphilis should be considered in any newborn with typical clinical manifestations even with low titres. Fluorescent antibody assays for antitreponemal IgM, which is not transferred across the placenta, have sometimes been used to confirm neonatal disease. Because non-treponemal tests can yield false-positive results, they should be confirmed with a specific treponemal test. However, any additional testing should not delay treatment in a high-risk or symptomatic infant.

Late congenital syphilis can be diagnosed by the clinical history, distinctive physical signs and serology. The Hutchinson triad of interstitial keratitis, Hutchinson incisors, and eighth cranial nerve deafness are diagnostic. Sometimes the nontreponemal test may be negative, but the fluorescent antibody test (FTA-ABS) should be positive. Syphilis should be considered in any infant with unexplained deafness, progressive intellectual deterioration, or keratitis.

**Treatment**

The treatment of early and late syphilis, and of syphilis diagnosed in pregnancy, is summarised in **Table 3**. Infants with confirmed or highly probable early congenital syphilis should receive aqueous crystalline penicillin G 50,000 units/kg IV twice daily for the first 7 days and 8-hourly thereafter for a total of 10 days, or procaine penicillin G 50,000 units/kg intramuscularly once/day for 10 days. If ≥1 day of therapy is missed, the entire course must be repeated. This regimen is also recommended for infants with possible syphilis if the mother fulfils any of the following criteria: (i) untreated; (ii) unknown treatment status; (iii) treated ≤ 4weeks before delivery; (iv) inadequately treated (e.g. non-penicillin regimen); or, (v) maternal evidence of relapse or reinfection (≥4-fold increase in maternal titres).

### In infants with possible syphilis (e.g. whose mothers were not adequately treated) but who are clinically well and have a completely negative evaluation, a single dose of intramuscular benzathine penicillin 50,000 units/kg is an alternative treatment option, but only if follow-up is assured, with non-treponemal serological testing monthly for the first three months and then at 6 months; treatment would then be initiated if the antibody titres rise or become positive at 6 months.

When congenital syphilis is diagnosed in older infants and children, other family members should be assessed for physical and serological evidence of infection. In the index case, a lumbar puncture should be performed before initiating treatment (aqueous crystalline penicillin G 50,000 units/kg IV every 4-6 hours for 10 days). A single dose of intramuscular benzathine penicillin G 50,000 units/kg may also be given at the end of treatment. Alternatively, if a full evaluation is completely negative and the child is asymptomatic, intramuscular benzathine penicillin G 50,000 units/kg once a week for three weeks may be offered. Many patients do not become seronegative but do have a 4-fold decrease in reagin antibody titres (e.g.VDRL). Patients should be re-evaluated at regular intervals to ensure appropriate serological response to therapy and early identification of any relapse.

Interstitial keratitis is usually treated by ophthalmologists with corticosteroid and atropine drops. There is some, albeit limited, evidence to treat patients with sensorineural hearing loss with penicillin with a corticosteroid such as oral prednisone 0.5 mg/kg once daily for 1 week, followed by 0.3 mg/kg once daily for 4 weeks, with gradual weaning over 2-3 months.12,13 Response to treatment may be less effective in patients with congenital syphilis and those or profound deafness.14 A recent, small case-series reported improved hearing and audiogram results in 9 (47%) and 7 (37%) of 19 patients with otosyphilis following a 21 day oral course of 400 mg/day doxycycline.15

**Follow-up testing**

Seropositive infants and those whose mothers were seropositive should have VDRL or RPR titres every 2-3 months until the test is non-reactive or the antibody titre has decreased 4-fold. In uninfected and in successfully-treated infants, nontreponemal antibody titres are usually nonreactive by six months of age. Passively-acquired syphilis antibodies may be present for longer, up to around 15 months of age. The same specific nontreponemal test should be used to monitor antibody titres in mothers and their infants over time. If VDRL or RPR remains reactive after 6-12 months or if syphilis antibody titres increase, the infant should be re-evaluated for clinical disease (including full blood count, lumbar puncture, long-bone x-rays, and other tests as clinically indicated).

**Prevention**

There is currently no vaccine available for prevention; the difficulties and obstacles in developing an effective vaccine against syphilis has been reviewed recently.16 Abstinence from intimate physical contact with an infected person will reduce syphilis transmission, as will proper use of a [latex condom](http://en.wikipedia.org/wiki/Latex_condom). Congenital syphilis can be prevented by screening and treating mothers during early pregnancy. Universal antenatal screening is recommended in most industrialised countries, and the [World Health Organization](http://en.wikipedia.org/wiki/World_Health_Organization) recommends all women be tested at their first antenatal visit and again in the [third trimester](http://en.wikipedia.org/wiki/Third_trimester). If they are positive, they recommend their partners also be treated.

In the UK, antenatal screening for syphilis is a well-established component of the Infectious Diseases in Pregnancy Screening Programme, which includes hepatitis B, HIV, syphilis and rubella. The UK-recommended screening includes a highly sensitive enzyme immunoassay (EIA) to detect antibodies, followed by confirmatory treponemal test (TPPA/ TPHA). The reported sensitivity and specificity of treponemal EIAs is high, ranging from 85-99.5% and 98.3-100%, respectively. Uptake of antenatal screening for syphilis in early pregnancy has consistently been high (>95%). During 2005-2012, of the 524,000-710,000 women screened, 0.15% (range 0.14-1.17%, equivalent to 834-1,171 women annually) were initially screened positive for syphilis but less than a third of them had an active infection that required treatment.17 The rest were subsequently identified as having evidence of resolved or treated syphilis. The incidence of congenital syphilis in a UK national surveillance study was 1.4/100,000 live-births and still-births in 2010 and 0.25/100,000 in 2011.18 Cases were mainly of white ethnicity and the influence of the eastern European syphilis epidemic was observed. Cases were generally identified in mothers who were unable to access healthcare service due to cultural barriers or chaotic lifestyles, and who experienced high levels of socioeconomic deprivation. Consequently, these mothers generally accessed clinical services around the time of delivery.19

**Conclusions**

Congenital syphilis is still very common in the developing world, as many women do not receive [antenatal care](http://en.wikipedia.org/wiki/Antenatal_care) or the antenatal care package does not include syphilis screening. In industrialised countries, congenital syphilis is rare but still occurs because those most likely to acquire syphilis are least likely to seek antenatal care. Transplacental transmission of syphilis, especially in the third trimester, is associated with a high rate of adverse outcomes, but the risks can be significantly reduced with early diagnosis (through antenatal screening, for example) and treatment in the first and second trimester, with careful management of the infant after birth.

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| **Primary Stage** | The primary stage typically presents with a single chancre (a firm, round, painless, non-itchy skin ulceration) usually at the site of infection and must be treated with appropriate antibiotics to prevent progression to later stages. Chancres can last for 3-6 weeks regardless of whether it is treated, but can be missed because it is painless.  |
| **Secondary Stage** | The secondary stage occurs 4-10 weeks after primary infection and is characterized by a diffuse symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, frequently involving the palms of the hand and soles of the feet. The rash may become macular, papular or pustular, and may affect the mucous membrane, where it may form flat, broad, whitish, wart-like lesions known as condyloma lata. Other symptoms include fever, sore throat, weight loss, hair loss and headache. Rarely, secondary syphilis may also be associated with inflammation of the liver, kidney, bone and joints, nerves and eyes. Symptoms of secondary syphilis usually resolve after 3-6 weeks, although they may recur in up to a quarter. A quarter to a half of the patients diagnosed with secondary syphilis do not report previously having had the classic chancre of primary syphilis. |
| **Latent Stages** | The latent phase is usually asymptomatic, with disappearance of all the primary and secondary symptoms. If left untreated, the latent phase can last anywhere between 3 and 30 years, but can be diagnosed by a blood test confirming serological evidence of disease. |
| **Tertiary Stage** | Around a third of untreated syphilis cases will go on to develop tertiary syphilis, which can be divided into three different forms: (i) **Gummatous syphilis** usually occurs 15 years after the initial infection, but can occur up to 50 years later. This stage is characterized by the formation of chronic [gummas](http://en.wikipedia.org/wiki/Gumma_%28pathology%29), which are soft, non-cancerous inflammatory growths contains dead and swollen fiber-like tissue. Gummata occur most often in the liver, but can also occur in the bone, brain, heart, skin, [testis](http://www.nlm.nih.gov/medlineplus/ency/article/002334.htm) and eyes. (ii) [**Neurosyphilis**](http://en.wikipedia.org/wiki/Neurosyphilis) affects the [central nervous system](http://en.wikipedia.org/wiki/Central_nervous_system) and can occur early (asymptomatic or syphilitic [meningitis](http://en.wikipedia.org/wiki/Meningitis)) or late (meningo-vascular syphilis, [general paresis](http://en.wikipedia.org/wiki/General_paresis), [tabes dorsalis](http://en.wikipedia.org/wiki/Tabes_dorsalis)). Late neurosyphilis typically occurs 4 to 25 years after the initial infection. Meningovascular syphilis is characterised by seizures. General paresis in late syphilis results from inflammation the brain, causing progressive dementia and paralysis. T[abes dorsalis](http://en.wikipedia.org/wiki/Tabes_dorsalis) (slow degeneration of the nerves primarily in the [spinal cord](http://en.wikipedia.org/wiki/Spinal_cord)) causes a range of symptoms, including [weakness](http://en.wikipedia.org/wiki/Weakness), [diminished reflexes](http://en.wikipedia.org/wiki/Hyporeflexia), intense shooting and burning pains, pricking sensations, joints damage and degeneration, [loss of coordination](http://en.wikipedia.org/wiki/Loss_of_coordination), personality changes, [urinary incontinence](http://en.wikipedia.org/wiki/Urinary_incontinence), [dementia](http://en.wikipedia.org/wiki/Dementia), [deafness](http://en.wikipedia.org/wiki/Deafness), and [visual impairment](http://en.wikipedia.org/wiki/Visual_impairment). Neurosyphilis is diagnosed by lumbar puncture showing high [white](http://en.wikipedia.org/wiki/Leukocytes) cell (predominately [lymphocytes](http://en.wikipedia.org/wiki/Lymphocytes)) and protein levels in the [cerebrospinal fluid](http://en.wikipedia.org/wiki/Cerebrospinal_fluid) in patients with known syphilis infection. (iii) **Cardiovascular** syphilis usually occurs 10–30 years after the initial infection and the most common complication is inflammation of the aorta (aortisit) which may results in formation of an aneurysm |

**Table 1. Characteristics of the different stages of syphilis infection**

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| **Blood tests:**  | Earlier serological studies such as the Wasserman and Kahn tests have been replaced my more sensitive and specific assays. Currently, blood tests are divided into [nontreponemal](http://en.wikipedia.org/wiki/Nontreponemal_tests_for_syphilis) and treponemal tests. (i) **Non-treponemal** tests (sensitivity, 71-100%; specificity, 98%) include the venereal disease research laboratory (VDRL) and [rapid plasma reagin](http://en.wikipedia.org/wiki/Rapid_plasma_reagin) (RPR) tests. These test are used initially to quantify antibodies which appear 4-8 weeks after infection and can help indicate successful treatment. (ii) **Treponemal** test, such as [treponemal pallidum particle agglutination](http://en.wikipedia.org/wiki/Treponemal_pallidum_particle_agglutination) (TPHA; sensitivity, 76-100%; specificity, 99%) or [fluorescent treponemal antibody absorption test](http://en.wikipedia.org/wiki/Fluorescent_treponemal_antibody_absorption_test) (FTA-Abs; sensitivity, 84-100%; specificity, 97%) are used to confirm the diagnosis following a positive non-treponemal test, which can occasionally yield [false positives](http://en.wikipedia.org/wiki/False_positive#Type_I_error) with some viral infections such as [varicella](http://en.wikipedia.org/wiki/Varicella) and [measles](http://en.wikipedia.org/wiki/Measles), lymphomas and connective tissue disease, tuberculosis, malaria, endocarditis, and pregnancy. Treponemal tests are reactive earlier (2-5 weeks after infection) and patients remain seroreactive for life, even if successfully treated. |
| **Direct testing:** | [Dark ground microscopy](http://en.wikipedia.org/wiki/Dark_field_microscopy) of [serous fluid](http://en.wikipedia.org/wiki/Serous_fluid) from a chancre can help confirm the diagnosis in up to 80% of cases, but requires experienced staff to perform the microscopy within 10 minutes of acquiring the sample. Chancre specimens can also tested by [direct fluorescent antibody](http://en.wikipedia.org/wiki/Direct_fluorescent_antibody) testing and PCR to detect specific syphilis genes, which are not as time-sensitive and do not require living bacteria for diagnosis. |

**Table 2. Investigations to confirm the diagnosis of syphilis**

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| **Early infections** | The first-choice treatment for uncomplicated syphilis remains a single dose of intramuscular [benzathine penicillin G](http://en.wikipedia.org/wiki/Benzathine_benzylpenicillin). [Doxycycline](http://en.wikipedia.org/wiki/Doxycycline) and [tetracycline](http://en.wikipedia.org/wiki/Tetracycline) are alternatives for penicillin allergics; however, because of the risk of birth defects ,they are not recommended for pregnant women. [Resistance](http://en.wikipedia.org/wiki/Antibiotic_resistance) to other antibiotics such as [macrolides](http://en.wikipedia.org/wiki/Macrolide), [rifampin](http://en.wikipedia.org/wiki/Rifampin) and [clindamycin](http://en.wikipedia.org/wiki/Clindamycin) is common. [Ceftriaxone](http://en.wikipedia.org/wiki/Ceftriaxone), a third-generation [cephalosporin](http://en.wikipedia.org/wiki/Cephalosporin) [antibiotic](http://en.wikipedia.org/wiki/Antibiotic), may be as effective as penicillin-based treatment. Sex should be avoided until the sores are healed.  |
| **Late infections** | Large doses of intravenous penicillin for a minimum of 10 days should be used to treat neurosyphilis because of the poor penetration of penicillin G into the [central nervous system](http://en.wikipedia.org/wiki/Central_nervous_system). Ceftriaxone or penicillin desensitization are alternatives if penicillin allergic. Other late presentations can be treated with once-weekly intramuscular penicillin G for three weeks. If allergic, doxycycline or tetracycline may be used as for early disease but for a longer duration. Treatment should limit further progression, but has minimal effect on any damage which has already occurred.  |
| Pregnant women | Pregnant women with early syphilis should receive a singlde intramuscular dose of benzathine penicillin G (2.4 million units). In the later stages of syphilis and for neurosyphilis, the same treatment as for nonpregnant patients is recommended. Occasionally, a Jarisch-Herxheimer reaction (a severe immunological reaction triggered by rapid release of toxic proteins from dead bacteria when antibiotic treatment commences) can occur and can lead to spontaneous abortion. Patients allergic to penicillin may be desensitized and then treated with penicillin. After adequate treatment, RPR and VDRL test results should decrease 4-fold by 6-12 months in most patients and revert to negative by 2 years in nearly all patients. Erythromycin therapy is inadequate for both the mother and fetus and is not recommended. Tetracycline is contraindicated. Retreatment in subsequent pregnancies is only needed if there is serological evidence of relapse or re-infection. Women who remain seropositive after appropriate treatment may have been re-infected and should be re-evaluated. A mother without the typical lesions of syphilis who is seronegative but who has had venereal exposure to a person with syphilis should be treated, because there is a 25-50% chance that she has acquired syphilis. |

**Table 3. Treatment of early and late infections as well as syphilis diagnosed in pregnancy**

**Key points**

1. In the UK and other industrialised countries, syphilis rates have been increasing in men and women since the 1980s.
2. Untreated syphilis in pregnancy has a high rate of transplacental transmission, with a 67% risk of pregnancy adverse outcomes compared to a background rate of 14%.
3. Diagnosis and treatment of syphilis in the first and second trimester of pregnancy significantly reduces the risk of adverse pregnancy outcomes back to baseline rates.

**References**

\* of special interest

\*\* of outstanding interest

1. WHO. Report on global sexually transmitted infection surveillance 2013. 2013.

2. Peterman TA, Su J, Bernstein KT, Weinstock H. Syphilis in the United States: on the rise? *Expert Rev Anti Infect Ther*. 2015;13(2):161-168. doi:10.1586/14787210.2015.990384.

3. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ*. 2013;91(November 2012):217-226. doi:10.2471/BLT.12.107623. \*

Large systematic review showing that the risk of serious adverse events in pregnancy is over 4 times greater in pregnant women with untreated syphilis than in pregnant women without syphilis.

4. Watson-Jones D, Changalucha J, Gumodoka B, et al. Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy. *J Infect Dis*. 2002;186:940-947. doi:10.1086/342952.

5. Newman L, Kamb M, Hawkes S, et al. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. *PLoS Med*. 2013;10(2):e1001396. doi:10.1371/journal.pmed.1001396.

6. Hawkes S, Matin N, Broutet N, Low N. Effectiveness of interventions to improve screening for syphilis in pregnancy: A systematic review and meta-analysis. *Lancet Infect Dis*. 2011;11(9):684-691. doi:10.1016/S1473-3099(11)70104-9.

7. Ishaque S, Yakoob M, Imdad A, Goldenberg RL, Eisele TP, Bhutta ZA. Effectiveness of interventions to screen and manage infections during pregnancy on reducing stillbirths: a review. *BMC Public Health*. 2011;11(Suppl 3):S3. doi:10.1186/1471-2458-11-S3-S3. \*\*

Systematic review showing that treatment of syphilis in pregnancy reduces the incidence of stillbirth by 80%.

8. Watson-Jones D, Gumodoka B, Weiss H, et al. Syphilis in pregnancy in Tanzania. II. The effectiveness of antenatal syphilis screening and single-dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes. *J Infect Dis*. 2002;186:948-957. doi:10.1086/342951. \*\*

Tanzanian study showing that treatment of syphilis in pregnancy reduces the risk of birth adverse outcome to the baseline rates.

9. Cheng JQ, Zhou H, Hong FC, et al. Syphilis screening and intervention in 500,000 pregnant women in Shenzhen, the People’s Republic of China. *Sex Transm Infect*. 2007;83(5):347-350. doi:10.1136/sti.2006.023655. \*\*

Recent large systematic review showing that the risk of birth adverse events is 2.2-fold greater if syphilis is treated in the third trimester of pregnancy compared to treatment during first and second trimesters.

10. Hawkes SJ, Gomez GB, Broutet N. Early antenatal care: does it make a difference to outcomes of pregnancy associated with syphilis? A systematic review and meta-analysis. *PLoS One*. 2013;8(2):e56713. doi:10.1371/journal.pone.0056713.

11. Muhammad G. Morshed. Current Trend on Syphilis Diagnosis: Issues and Challenges. *Adv Exp Med Biol*. 2014;808:51-64. doi:10.1007/978-81-322-1777-0.

12. Gleich LL, Linstrom CJ, Kimmelman CP. Otosyphilis: A diagnostic and therapeutic dilemma. *Laryngoscope*. 1992;102(11):1255-1259. doi:10.1288/00005537-199211000-00010.

13. Zoller M, Wilson WR, Nadol JB. Treatment of syphilitic hearing loss. Combined penicillin and steroid therapy in 29 patients. *Ann Otol Rhinol Laryngol*. 1979;88(2 I):160-165.

14. Dobbin JM, Perkins JH. Otosyphilis and hearing loss: response to penicillin and steroid therapy. *Laryngoscope*. 1983;93(12):1540-1543.

15. Chotmongkol V, Sawanyawisuth K, Yimtae K, Chantarojanasiri T, Chotmongkol R. Doxycycline treatment of otosyphilis with hearing loss. *Sex Transm Infect*. 2012;88(3):177-178. doi:10.1136/sextrans-2011-050201.

16. Cameron CE, Lukehart SA. Current status of syphilis vaccine development: Need, challenges, prospects. *Vaccine*. 2014;32(14):1602-1609. doi:10.1016/j.vaccine.2013.09.053. \*\*

Thorough review of the need for a syphilis vaccine and current progress in its development.

17. England PH. National Antenatal Infections Screening Monitoring . Data tables : England 2005 - 2013 Table 1 : Contents. 2013.

18. Simms I. Annual Report 2013-2014. 2014;(1057744):11-12.

19. Health Protection Report. HIV-STIs Recent epidemiology of infectious syphilis and congenital syphilis Recent epidemiology of infectious syphilis in England. 2013;7(44):0-3.