INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
2024, Vol. 0(0) 1–13

DOI: 10.1177/09564624241280387
journals.sagepub.com/home/std
Sage

British Association of Sexual Health and HIV (BASHH) UK guidelines for the management of syphilis in pregnancy and children 2024

Margaret Kingston[1], Janet Wilson[2], Sarah Dermont[3], Helen Fifer[4], Koon Chan[5], Hermione Lyall[6], Paddy McMaster[7], Emma Shawkat[5] and Alex Thomas-Leech[8]

Abstract

This new guideline details the specific management of syphilis in pregnancy and in children. It is to be used in clinical practice alongside the BASHH UK guidelines for the management of syphilis 2024.

Keywords

Syphilis (*Treponema pallidum*), Europe

Date received: 29 July 2024; accepted: 5 August 2024

Objectives

The main objective of these guidelines is to reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI or undergoing investigation for possible infection.

Specifically the guidelines offer recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of syphilis in pregnancy and in children, the management of the initial presentation is covered, as well as how to prevent transmission and future infection. In addition the management of older children diagnosed with syphilis is described.

The guidance has been developed for those working in level 3 genitourinary medicine, antenatal and paediatric services. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

The initial part of these guidelines will focus on management of pregnant women and people with positive tests for syphilis, the latter on the management of their babies.

Methods

The guidelines writing group followed the British Association for Sexual Health and HIV (BASHH) Framework for Guideline Development.[1]

Search strategy

A systematic literature review was undertaken. Medline, Embase and the Cochrane Library were searched for English language publications using the following terms: (i) syphilis AND (perinatal OR neonatal OR congenital OR 'vertically acquired' OR paediatric) – only randomised controlled trials published up to December 2020; and (ii) (syphilis OR (syphilis AND HIV)) AND (perinatal OR pregnant/pregnancy OR congenital OR maternal) – all

[1] Consultant Physician Genitourinary Medicine, Manchester University NHS Foundation Trust, Manchester, UK
[2] Leeds Teaching Hospitals NHS Trust Consultant Physician Genitourinary Medicine, UK
[3] Infectious Diseases in Pregnancy Screening Programme, NHS England, UK
[4] Consultant Microbiologist, UK Health Security Agency, UK
[5] Consultant Obstetrician Manchester University NHS Foundation Trust, Manchester, UK
[6] Consultant Paediatric Infectious Diseases, Imperial College Healthcare NHS Trust, London, UK
[7] Consultant Paediatric Infectious Diseases, Manchester University NHS Foundation Trust, Manchester, UK
[8] Specialist Midwife, Manchester University NHS Foundation Trust, Manchester, UK

Corresponding author:
Margaret Kingston, Consultant Physician Genitourinary Medicine, Manchester University NHS Foundation Trust, The Hathersage Centre, 280 Upper Brook Street, Manchester M13 0FH, UK.
Email: margaret.kingston@mft.nhs.uk

studies published between January 2014 and December 2020.

Equality impact assessment and considerations

Equality impact assessment was completed using the National Institute for Health and Care Excellence tool (see Appendix 1).

Throughout this guidance we use current guidance regarding language recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) to promote consistency, fairness and inclusivity to communicate with range of audiences.

Stakeholder involvement, piloting and feedback

The document was reviewed by the Clinical Effectiveness Group, the Public Panel and the National Audit Group of BASHH, and their comments incorporated. The draft guidelines were placed on the BASHH website and any comments received after 2 months were reviewed by the authors and acted on appropriately. The document was also piloted by target users and the public panel of BASHH, and their feedback considered by the authors.

Aetiology, transmission and epidemiology

Treponema pallidum readily crosses the placenta and vertical transmission can occur at any stage of pregnancy. The risk of transmission varies with syphilis stage and is greatest in early disease.[2,3] Accordingly, transmission was associated with rapid plasma reagin (RPR) titres ≥1:8 (risk ratio 18.1, $p < .001$) in one cohort study.[4]

Transplacental spread is increased during the second half of pregnancy, especially in the third trimester.

Adverse pregnancy outcomes can be significantly reduced with early detection and treatment in the first and second trimesters, along with careful management of the infant.[5]

Approximately 700,000 women and pregnant people are screened for syphilis in pregnancy each year in England. In the reporting year 2019–2020, 410 individuals had a positive antenatal screening test for syphilis that required treatment.[6]

A review of suspected and confirmed congenital syphilis in England in babies born between January 2015 and June 2020 identified 65 cases.[7] Of these, 24 infants were confirmed to have congenital syphilis, and 41 were suspected cases that had been treated and/or tested due to inadequate or unconfirmed maternal treatment during pregnancy.

In contrast to a previous review of congenital syphilis,[8] this recent review[7] found that most of the birth parents (21/24, 87.5%) were UK born. Median maternal age was 22 years at delivery. Almost all pregnant people were of white ethnicity (23/24, 95.8%). Adverse social circumstances during pregnancy were reported in more than half of cases, with many experiencing multiple issues.

For all 24 infants diagnosed with confirmed congenital syphilis, antenatal screening had been offered and accepted.

For 15 infants, the pregnant person had negative antenatal screening results, meaning they became infected with syphilis later during their pregnancy and were undiagnosed and untreated before giving birth, with the majority being diagnosed following their symptomatic infant's diagnosis.

Among the nine people who had a positive antenatal screening result, four were untreated; of these, one was only diagnosed during labour and three did not attend their referral appointment at a sexual health service. Of the five who attended sexual health services following referral, two had been booked late for antenatal care (>30 weeks' gestation) and delivered before the treatment was fully effective; two reported a penicillin allergy and were treated with an inappropriate alternative antibiotic; and one was successfully treated but became reinfected during the pregnancy. The latter cases highlight the need to consider carefully treatment options and follow-up for diagnoses in pregnancy where penicillin allergy is reported and the need to reinforce messages about protected sex during pregnancy, as well as the importance of testing and treatment of partners so that all are aware of the risk of reinfection.

Screening requirements in pregnancy

The UK National Screening Committee recommends that population screening for syphilis is offered and recommended to all pregnant women and people. This is to enable early detection and treatment of syphilis in order to significantly reduce the risk of vertical transmission.

The Infectious Diseases in Pregnancy Screening (IDPS) programme has responsibility for implementing this policy.[9] The programme sets measurable standards of care and offers guidance and resources for professionals to support the delivery of the screening programme. The objectives of the programme are to:

- Reduce the risk of vertical transmission of syphilis
- Ensure that syphilis is identified early in pregnancy
- Facilitate appropriate and timely neonatal referral and management.

IDPS guidelines state that all pregnant people should be offered and recommended screening for syphilis in every pregnancy, irrespective of any past results or treatment in previous pregnancies.

During the pre-test discussion, all should be made aware of the reasons why screening for syphilis in pregnancy is recommended. The NHS 'Screening tests for you and your baby' resource is available in a large number of languages and should be used to support this discussion.[10]

Where screening is accepted, blood samples should be taken at the earliest opportunity and not deferred to coincide with a later appointment. Where screening is declined, a formal re-offer should be made by the antenatal screening team within the timeframes specified in the IDPS programme guidance.[11]

Screening for syphilis can be undertaken at any point during pregnancy. Urgent screening should be offered and recommended to those who present for care at a later stage of pregnancy, or in labour, with no reliable screening results from a UKAS-accredited laboratory. For urgent screening, direct liaison with the laboratory is vital to ensure there is necessary clinical information to inform prompt analysis and communication of results.

In the antenatal setting, positive screening results should be communicated directly to the screening team by the laboratory. Results should be communicated by the screening team without delay and an immediate referral should be made to sexual health services for timely assessment.

When giving negative syphilis screening results, midwives should advise people that they are negative at the point of screening and that this does not confer protection throughout pregnancy. They should be advised about the importance of protecting themselves from infection and encouraged to request a test if they feel they have been at risk of infection at any stage of pregnancy or in the 3 months prior to the negative screening result.

The screening team and wider midwifery teams should be vigilant for the need to offer a repeat test when a patient:

- Reports a change in sexual partner
- Is, or has a partner who is known to be, sexually active with other people
- Injects recreational drugs
- Is a sex worker
- Has a partner who is known to have HIV or hepatitis
- Is diagnosed or has a partner who is diagnosed with a sexually transmitted infection (STI)
- Has any symptoms of an STI

Sometimes initial positive screening results (i.e. positive treponemal antibody test using enzyme immunoassay [EIA] or chemiluminescent immunoassay [CLIA]) fail to confirm on further testing with a different treponemal test (e.g. *T. pallidum* haemagglutination assay [TPHA] or a second EIA/CLIA). In the UK most pregnant women and people are at low risk of syphilis, and these discrepant results are usually false positive due to non-specific cross-reaction. However, it is prudent to request a second sample, 2 weeks after the initial sample, to exclude the possibility of very early infection. This can cause anxiety and people should be reassured that most of these repeat tests essentially confirm that the screening test was a false-positive result and they do not necessarily need referral or treatment.

Healthcare professionals involved in screening must be familiar with the IDPS screening pathway and specified timeframes for actions to be undertaken as set out in the programme guidance.[9] Further information can be found in the IDPS laboratory[12] and screening[11] handbooks and should be used in conjunction with these clinical guidelines.

Professionals involved in screening for syphilis in pregnancy are also recommended to complete the IDPS eLearning resource, available from Health Education England.[13]

Antenatal management

Management of positive syphilis screening results and referral to sexual health services is the responsibility of the antenatal screening team and should be undertaken in line with the national IDPS guidance.[9]

On receipt of a confirmed positive result from the laboratory, the antenatal screening team should contact their patient to inform them of the result. This discussion should be undertaken sensitively and include the provision of information about the infection, its relevance to their health and pregnancy and what to expect next, including a referral to GUM for further assessment. This discussion enables the screening team to:

- Collect information to support onward referral to GUM
- Promote engagement with GUM
- Identify and address any additional needs such as an interpreter to support the assessment
- Provide contact details for the screening team for further support and liaison

Multidisciplinary working. The management of syphilis infection in pregnancy involves several specialities and therefore effective multidisciplinary working is needed. It is important to have clear and timely communication between professionals and robust working relationships to ensure that high-quality care can be delivered. Membership of the multidisciplinary team (MDT) will vary locally and may include some or all of the following:

- Screening team/specialist midwife
- GUM services
- Paediatrics/neonates
- Obstetrics
- Microbiology/virology

The prevalence of syphilis varies, and in some units the number of cases may be very low and it may not be feasible to hold regular face-to-face MDT meetings. Instead, it may be preferable to hold virtual meetings or join existing forums such as neonatal or HIV MDT meetings which have well-established working relationships. It is important that, regardless of the number of cases, each is managed collaboratively. Members of the screening team are crucial to

the success of the working of the MDT and central to its coordination.

Collaborative working with the screening laboratory. Screening teams and laboratories should have clear communication processes in place to ensure that positive results are relayed to screening midwives in a timely manner as per the national screening standards. Links with the laboratory are fundamental to collaborative working to ensure appropriate management and timely interventions in partnership with patients.

Care plans. The BASHH Syphilis Birth Plan or a local adaptation (Appendix 2) should be used for all cases of confirmed syphilis in pregnancy as it enables the transfer of key information between professionals regarding the woman or pregnant person's treatment and the requirements for the infant at birth. There should be a neonatal alert or similar process to signpost professionals to the plan at delivery. The screening team should ensure that birth plans and neonatal alerts are established before delivery.

Promoting sexual health in pregnancy. Midwives can promote sexual health during pregnancy and have an important role in 'negative now' messaging to raise awareness of the ongoing risk of infection in pregnancy following a negative screening result at booking. The screening team should support this message during follow-up contact and support re-testing for anyone who feels that she may have been at risk.

Management in pregnancy: general considerations

The main goals of syphilis treatment in pregnancy are:

- Eradication of parental disease and prevention of reinfection
- Prevention of vertical transmission
- Treatment of any existing fetal infection.

All pregnant women and people should have serological screening for syphilis as part of their first antenatal assessment. Tests should be repeated later in pregnancy if a patient may have been at risk of infection during the test window period (3 months) or after a negative initial screening result, or if they have any symptoms or signs of syphilis. Such cases should be discussed with a local GUM physician.

Adverse pregnancy outcomes in syphilis. Although fetal infection usually occurs late in pregnancy, it has been demonstrated as early as 8–9 weeks of gestation.[14] This may result in fetal growth restriction, polyhydramnios, fetal anaemia, hepatosplenomegaly, intrahepatic calcifications and hydrops fetalis (oedema in two or more fetal compartments, e.g. ascites, pleural effusion, pericardial effusion and skin oedema). Infection can subsequently lead to miscarriage, preterm labour and stillbirth, and may also be associated with placentomegaly due to placental oedema. These adverse pregnancy outcomes can be significantly reduced with early detection and treatment in the first and second trimesters, along with careful management of the infant.[5]

Significance of positive treponemal serology in pregnancy. In 2021 in the UK, 1.59 per 1000 women and pregnant people had positive antenatal screening tests.[15] Of these:

- A total of 390 (43.0%) who screened positive required treatment
- Among those requiring treatment, 92.1% (359) received treatment in pregnancy.

The majority of those who were treated received benzathine penicillin (343 of 359; 95.5%), in line with BASHH syphilis guidance.[16]

Six were incorrectly treated with only macrolides. For these six pregnancies, the outcomes were:

- Two infants with confirmed congenital syphilis
- One stillbirth with confirmed congenital syphilis
- Two infants with no evidence of congenital syphilis
- One woman lost to follow-up prior to delivery (believed to have gone abroad).

Management of positive maternal treponemal serology. It is important that referrals of pregnant women and people with positive screening test results are prioritised and, where necessary, are seen as quickly as possible by a GUM physician. Assessments may be undertaken either face to face or virtually, to be determined by the physician, based on clinical history and the woman's needs. Assessment of those who book late (>20 weeks' gestation) should be expedited because of an increased preterm delivery risk in this population.

It is recommended that GUM services have a named clinician to facilitate referrals and ongoing liaison with maternity services. GUM physicians who have limited or infrequent experience of managing syphilis in pregnancy should seek advice from more experienced colleagues or from clinical networks.

All those with confirmed positive screening test results should be considered infected unless an adequate treatment history and treatment response can be confirmed by a clinician or service. Negative RPR titres do not necessarily indicate previous adequate treatment as these tests can be negative in very early or in late syphilis.

For those without a confirmed history of treatment, syphilis should be staged as early (within 2 years of acquisition) or late (more than 2 years since acquisition) in order to determine the recommended penicillin regimen. Clinical lesions, compatible with primary and secondary syphilis and/or that are *T. pallidum* dark ground microscopy or polymerase chain reaction (PCR) positive, indicate early disease. In women with no signs, the only way of confirming early infection is a negative syphilis

serology test within the past 2 years. If such negative results are not available, the patient must be assumed to have late syphilis and treated accordingly.

Management where syphilis was cured prior to the current pregnancy. RPR titres should be checked at the first antenatal booking appointment and repeated later in pregnancy if there is a risk of reinfection. If the RPR titre indicates no reinfection, then no further treatment is required and there is no need for the neonate to undergo testing for syphilis.

Referral to fetal medicine. Where syphilis is treated in the current pregnancy, particularly for early infection, and the routine fetal anomaly scan shows evidence of possible congenital syphilis infection, maternal referral to the local fetal medicine centre is recommended. Fetal congenital syphilis infection may be suggested by ultrasound scan detection of non-immune hydrops or hepatosplenomegaly. Fetal assessment will help in the planning of antepartum care as well as neonatal treatment.

Retreatment of women with a history of syphilis treated before conception. Retreatment should be considered:

- When there is lack of confirmation, or uncertainty about the adequacy, of treatment
- In the absence of serological cure (a 4-fold drop in RPR titre, e.g. from 1:16 to 1:4). Where low-level RPR titres are present at baseline, this drop may not occur and the titres may remain serofast.

Maternal diagnosis

It is vital that GUM physicians make a clear maternal diagnosis and communicate this to the MDT. A template for a syphilis birth plan can be found in Appendix 2.

Maternal treatment may or may not be indicated.

Maternal treatment *not indicated*

- Biological false-positive result
- Syphilis adequately treated before this pregnancy

Maternal treatment *indicated*

- Active syphilis of any stage
- Unclear history of syphilis treated before the current pregnancy.

Maternal treatment

Patients should be treated appropriately for the stage of disease, according to the BASHH UK national guidelines on the management of syphilis 2023.[16] Limited evidence suggests that a second dose of *benzathine* penicillin G 1 week after the first may be beneficial for fetal treatment in pregnant women or people with early syphilis,[17–19] and in pregnancies with sonographic signs of fetal or placental syphilis as this indicates a greater risk of fetal treatment failure.[20]

Physiological changes in pregnancy alter drug pharmacokinetic parameters and may cause reduced plasma penicillin concentrations.[21]

For these reasons, when treatment for early syphilis is initiated in the third trimester, a second dose of benzathine penicillin G is recommended 1 week after the first, with careful assessment of the *neonate* at birth.

Parenteral penicillin G is the only therapy with proven efficacy for the treatment of syphilis in pregnancy. The non-penicillin alternative is ceftriaxone, for which limited data are available.[22]

Macrolides should not be used because of high levels of macrolide resistance, treatment failures and adverse pregnancy outcomes have been reported.[15] Pregnant women and people who report allergy to penicillins should have a thorough drug allergy history taken with substantiation from primary care if needed. If a true allergy is confirmed, an urgent referral to immunology/allergy services is required for allergy testing to penicillin and ceftriaxone.

In the absence of allergy to penicillin, standard benzathine penicillin G treatment should be given.

If a patient is allergic to penicillin but not ceftriaxone, ceftriaxone can be used or penicillin desensitisation and immediate penicillin treatment can be considered. This should be undertaken in conjunction with the GUM, obstetric and paediatric teams.[23]

A systematic review of pregnant women with a history of penicillin allergy found that 84% had a negative penicillin skin test. Allergy-related reactions were rare with penicillin skin testing and penicillin challenge. Reactions occurred in 20% undergoing desensitisation but most were benign, and only one adverse pregnancy outcome was reported.[23] This confirms that penicillin skin testing and desensitisation can be safely undertaken during pregnancy.[23]

In the case of soya or peanut allergy, refer for allergy testing or treat with procaine penicillin or ceftriaxone.

Patients should be managed in close liaison with obstetric, midwifery and paediatric colleagues.

In pregnancy the rate of the Jarisch–Herxheimer reaction was thought to be the same as in non-pregnant women or people (~40%) based on small series[24,25] but it may be lower than previously reported.[26] The reaction is thought to be secondary to an acute inflammatory reaction due to large numbers of the spirochaetes being killed resulting in an excessive release of cytokines. In addition, the pregnant woman may experience uterine contractions (~40%–65%) and fetal heart rate abnormalities (~40%) on cardiotocography which resolve within 24 h of maternal penicillin treatment. In one series, no fetuses required delivery because of fetal heart rate abnormalities.[25] Therefore, there may be a theoretical increased risk of spontaneous and

iatrogenic preterm delivery and fetal death associated with the Jarisch–Herxheimer reaction, though these complications are also associated with maternal and fetal congenital syphilis infection. The Jarisch–Herxheimer reaction is generally self-limiting and treatment in pregnancy should be supportive, as in all patients, with antipyretics and fluids. There is no evidence that administration of high-dose oral prednisolone will reduce the occurrence of uterine contractions or fetal heart rate abnormalities.

If syphilis treatment is completed less than 4 weeks prior to delivery, the infant should be given treatment for congenital syphilis at birth. Infants born to those treated with macrolides, or who are untreated or inadequately treated, should also be given treatment for congenital syphilis at birth.

Partner notification, with testing and treatment of the sexual partner, is an essential part of treatment to prevent reinfection. Clear advice about the period of sexual abstinence should be given.

Maternal follow-up after treatment. Follow-up serological testing should be undertaken according to the BASHH UK national guidelines on the management of syphilis 2024.[16] It may take several months to observe a 4-fold drop in RPR titre and in many pregnancies delivery will occur beforehand. Moreover, those with late syphilis may have serofast RPR titres. Hence, serological cure may not be demonstrable before the birth of the neonate. If a pregnant person is at risk of reinfection repeat serology could be performed more regularly to monitor for reinfection and enable rapid retreatment if needed.

Serological testing may be helpful at delivery to identify reinfection and to aid the diagnosis of congenital syphilis.

Recommendations

All pregnant people should have syphilis serology at their first antenatal clinic visit, and re-screening later in pregnancy should be offered if a risk of syphilis is recognised: 1A.

When patients have been cured of syphilis prior to pregnancy, and are not at risk of reinfection, the neonate will not require testing: 1B.

Retreatment in pregnancy is indicated where there is uncertainty of adequate treatment: 1B.

Treatment of syphilis should be as appropriate for the stage of treatment (see BASHH guidelines): 1B.

For those allergic to penicillin, desensitisation should be considered: 1C.

Patients should be managed in conjunction with fetal medicine and paediatric colleagues. Routine use of steroids to prevent the Jarisch–Herxheimer reaction is not recommended: 1C.

If maternal syphilis treatment is completed less than 4 weeks prior to delivery, the infant should be given treatment for congenital syphilis at birth: 1C.

Partner notification, with testing and treatment of the sexual partner, should be undertaken: 1C.

Maternal diagnosis and treatment should be clearly communicated to the appropriate obstetrician, GP and paediatric team, with informed consent; a template birth plan is provided: 1C.

Follow-up serological testing should be undertaken according to the BASHH UK national guidelines on the management of syphilis 2023.[16] However, if a patient is at risk of reinfection (i.e. their sexual partner has not been tested/treated for syphilis), repeat serology could be performed more regularly to monitor for reinfection and enable rapid retreatment if needed: GPP.

Serological testing may be performed at delivery to identify reinfection and to aid the diagnosis of congenital syphilis: GPP.

Congenital syphilis

Congenital syphilis may present early (in the first 2 years of life) or late (after 2 years of age).[27–30] Transmission is usually via the placenta but can occur during delivery if maternal genital lesions are present. The presence of signs at the time of delivery is dependent on the duration of maternal infection and the timing of treatment. Around two-thirds of infants with congenital syphilis will be asymptomatic at birth but most will develop signs within the first few weeks of life (signs and symptoms of congenital syphilis are shown in Table 1).[31]

Between 2015 and 2020 there were 25 diagnoses of congenital syphilis in England. Most patients were from a white ethnic group and either British or Romanian. A review of these cases identified contributing factors including social vulnerabilities and chaotic lifestyles, late presentation for antenatal care and poor engagement with services.[32]

Surveillance of congenital syphilis has been strengthened since 2019 with the establishment of Integrated Screening Outcomes Surveillance Service (ISOSS) as part of the IDPS programme and annual reporting.[15]

Diagnosis of congenital syphilis

Diagnosis of congenital syphilis can be very difficult; most infected neonates appear normal at birth and passive transfer of maternal syphilis antibodies may cause reactive neonatal serology in the uninfected infant. Given these difficulties, it is important that paediatricians and GUM physicians work closely when managing neonates. All children born to those with positive treponemal serology require clinical evaluation and syphilis serological tests, unless the maternal result is confirmed to be a false-positive result in pregnancy, or when syphilis was cured prior to this pregnancy (see Tables 2 and 3 for interpretation of serological and other laboratory tests). However, it is noteworthy that third-trimester repeat

Table 1. Signs and symptoms of congenital syphilis.

a. Early syphilis	
Common manifestations are in bold (in 40%–60% of cases)	
General	Low birth weight, prematurity,[53] non-immune hydrops, pyrexia
Haematological	Generalised lymphadenopathy, hepatosplenomegaly, jaundice, anaemia (can be haemolytic), thrombocytopenia
Skin	Rash (usually maculopapular, but almost any form of rash is possible, may be a blueberry muffin rash), the palms and soles may be red, mottled and swollen, vesiculobullous lesion, condylomata lata (flat, wart-like plaques in moist areas such as the perineum), peri-oral fissures, severe desquamation (often of hands/feet)
Mucous membranes	Haemorrhagic rhinitis (bloody snuffles), ulceration of the nasal mucosa, mucous patches
Neurological	Meningitis, microcephaly, hydrocephaly, intracranial calcification, sensorineural deafness, failure to move an extremity (pseudo-paralysis of Parrot)[49]
Ocular	Cataracts, corneal scarring, glaucoma, chorioretinitis, microphthalmia
Skeletal	Osteochondritis,[54,55] periosteitis (elbows, knees, wrists)
Liver	Hepatosplenomegaly, jaundice (may be conjugated), hepatitis
Other	Multi-organ failure, glomerulonephritis, pneumonitis
b. Late syphilis[56]	
Signs develop as a result of chronic and persistent inflammation resembling gummatous disease in adults. Hutchinson's triad: abnormal teeth, deafness and interstitial keratitis	
Dental	Hutchinson's incisors (small widely spaced, peg-shaped, notched incisors), hypoplastic enamel, mulberry molars (maldevelopment of cusps of first molars)
Skeletal	Frontal bossing, short maxilla, high palatal arch, saddle nose deformity, protuberance of mandible, sternoclavicular thickening, Clutton's joints (painless, symmetric hydrarthrosis of the knees and elbows)
Skin	Rhagades (peri-oral fissures)
Neurological	Intellectual disability, cranial nerve palsies, sensorineural deafness
Eye	Interstitial keratitis, phthisis bulbi[57] (atrophic eye)
Renal	Paroxysmal cold haemoglobinuria

syphilis testing is not routinely undertaken in the UK, so new infections or reinfections may not be detected.

Birth plan

A shared birth plan, initiated antenatally by the GUM team treating the mother or pregnant person, is essential to promote communication and guide neonatal management.

Maternal factors that may increase or decrease the risk of vertical transmission of syphilis are shown in Table 4.

Risk of congenital syphilis

Depending on whether maternal treatment has been completed in pregnancy, there may be no risk of congenital syphilis, or the risk may be low or high.

Congenital syphilis: no risk. There is no risk of congenital syphilis for a neonate who has a normal physical examination and the mother or pregnant person:

- Was treated before pregnancy, with treatment that was appropriate for the stage of infection and
- Has no new risk of re-infection

No investigations are required for infants at no risk of congenital syphilis.

Congenital syphilis: low risk. There is a low risk of congenital syphilis for any neonate who has a normal physical examination and the parents:

- Were treated during pregnancy, with treatment that was appropriate for the stage of infection and
- Were treated >4 weeks before delivery and
- Have no evidence of reinfection or relapse.

For infants at low risk of congenital syphilis, maternal and infant (not cord blood) syphilis serology are required; treponemal, non-treponemal and syphilis IgM. The infant should be allowed home with follow-up tests in clinic at 3 months.

If RPR and IgM negative at 3 months, can discharge.

If RPR titre falling but still positive, repeat at 6 months.

If RPR titre unchanged from birth or rising or IgM positive, refer to local paediatric infection specialists or consult GUM.

Congenital syphilis: high risk. There is a high risk of congenital syphilis for any neonate when maternal treatment:

- Was <4 weeks prior to delivery or
- Was with non-beta-lactam regimens or
- Was incomplete or
- Was inadequate or
- Is uncertain.

Table 2. Guide for interpretation of syphilis serological test results of mothers and their infants.[27,58–60]

Non-treponemal test (RPR)		Treponemal test (such as EIA)[a]		
Maternal	Infant	Maternal	Infant	Interpretation
–	–	–	–	No syphilis or incubating syphilis detected
+	+	–	–	No maternal syphilis (false-positive non-treponemal test with passive transfer to the infant)
+	+/–	+	+	Maternal syphilis with possible infant infection; or a maternal infection treated during pregnancy; or maternal latent syphilis and possible infection of the infant
+	+	+	+	Recent or previous maternal syphilis; possible infection in the infant
–	–	+	+	Syphilis treated before or early in pregnancy; or another spirochaetal disease e.g. Lyme, yaws or pinta (i.e. false-positive serology)

[a]Neonatal IgM: indicates neonatal infection.

Table 3. Guide for interpretation of infant laboratory tests.

Treponemal IgM	A positive treponemal IgM test supports a diagnosis of congenital syphilis, but must be interpreted in conjunction with the history, clinical signs and results of other syphilis blood tests A negative IgM test does not exclude infection as the IgM response may be delayed or suppressed in infants
RPR	Passive transplacental transfer of maternal IgG antibodies may cause a false-positive RPR test result in the newborn but this usually reverts to negative by 6 months A positive RPR test result at a titre of ≥4-fold that of maternal supports a diagnosis of congenital syphilis, and should be repeated. Note a lower RPR titre does not exclude the diagnosis. Maternal and infant samples should be tested as a pair
CLIA/EIA total antibody and TPHA/TPLA	CLIA/EIA and TPHA/TPLA are tests for specific treponemal antibodies; these IgG antibodies will be detectable long term in any person who has had a spirochaetal infection (e.g. syphilis, yaws, pinta). The titre may increase with reinfection Passive transplacental transfer of maternal IgG antibodies will be detected in the newborn, but the tests will usually be negative by 12–18 months
Full blood count	May show non-haemolytic anaemia, leucocytosis or leucopenia, thrombocytopenia, polychromasia or erythroblastaemia
Liver function tests/ transaminases	Syphilitic hepatitis may cause elevated levels of alkaline phosphatase, aspartate aminotransferase/ alanine aminotransferase or bilirubin. There may also be conjugated hyperbilirubinaemia
Urea and electrolytes, creatinine	Syphilis can cause glomerulonephritis resulting in uraemia
PCR	PCR can be performed on swabs from ulcers, nasal discharge, mucous membrane lesions or moist skin rashes, as well as throat swabs and naso-pharyngeal aspirates. PCR on placental tissue, neonatal blood and CSF can also be considered
Dark ground microscopy	Ulcers, nasal discharge, mucous membrane lesions or moist skin rashes can be sampled and used to directly visualise *T. pallidum*. However, specimen collection and microscopy require prior training. Microscopy should take place as soon as possible after the specimen is obtained. Contact the GUM team for help performing dark ground microscopy
Placenta	The syphilitic placenta may appear macroscopically normal. If the fetus is severely affected by syphilis, the placenta may appear paler, larger and thicker than normal Histology and/or PCR of the placenta and cord may provide evidence of congenital infection
Radiology	In congenital syphilis, most bone lesions are not clinically apparent. However, osteochondritis, periostitis and osteomyelitis are frequently present, most often in the long bones and ribs Periostitis of the skull can produce frontal bossing on X-ray

Table 4. Maternal factors and risk of congenital syphilis.

Decreasing neonatal risk	Increasing neonatal risk
Treatment completed	Partial or no treatment[a]
Treated with penicillin or ceftriaxone	Treated with non-beta-lactam[a]
Treatment completed >30 days pre-delivery	Treatment <30 days before delivery[a]
Late latent maternal syphilis	Primary/early maternal syphilis
4-fold drop in RPR achieved	4-fold drop in RPR not achieved

[a]The presence of any one of these three factors constitutes inadequate maternal treatment and requires treatment of the infant at birth. Congenital syphilis may still occur despite the absence of any of these three factors.

See Table 5 for details about investigations for infants at high risk of congenital syphilis.

Laboratory tests for congenital syphilis

The presence of *T. pallidum* can be demonstrated directly by dark field microscopy or PCR of exudates from suspicious lesions or body fluids, e.g. nasal discharge or naso-pharyngeal aspirates[33]. PCR of placenta, neonatal blood and CSF may be considered.[34,35]

Serological tests should be performed on the infant's blood (not cord blood). Perform treponemal and non-treponemal antibody tests in parallel. Serological tests detecting treponemal and non-treponemal IgG antibodies may be positive due to passive transfer of maternal antibodies whether or not the infant is infected.

Definition of congenital syphilis

Possible case. Maternal untreated or inadequately treated syphilis at delivery and a reactive serum RPR test in the infant but no other features of probable or confirmed congenital syphilis (requires treatment).

Probable case. Maternal untreated or inadequately treated syphilis at delivery, a reactive serum RPR in the infant and at least one of the following:

- Any evidence of congenital syphilis on physical examination
- Any evidence of congenital syphilis on radiographs of long bones
- A positive CSF RPR test
- Infant's RPR titre ≥4-fold that of the mother

Note a lower RPR titre does not exclude the diagnosis; most infants with congenital syphilis have an RPR titre that is the same or one or two dilutions less than the maternal titre.[36–38]

Confirmed case. A probable case plus at least one of the following:

- Demonstration of *T. pallidum* by darkfield microscopy or PCR of the umbilical cord, placenta, neonatal nasal discharge, body fluids or skin lesion material
- Detection of *T. pallidum*-specific IgM

Recommendation

Infants with possible signs of congenital syphilis require appropriate evaluation and testing in conjunction with maternal serological tests for syphilis and treatment history: 1A.

Treatment of congenital syphilis. If dosing is missed for >24 h, treatment must be restarted as treponema can rapidly re-grow.[39] Ceftriaxone is suitable for ambulatory care for 10–14 days, if hospital admission is not possible. There are no studies of ceftriaxone treatment for congenital syphilis, but observed response rates are equal to that of penicillin in adults.[30,40–48]

In infants/children, intravenous therapy is preferable, to avoid the pain associated with intramuscular injections. See Table 6 for treatment of congenital syphilis.

If CSF white cell and protein levels are raised and RPR is positive, treat for 10 days and repeat lumbar puncture at 6 months.[49,50]

Congenital syphilis: late diagnosis

Recommendations

Congenital syphilis diagnosed at ≥2 years of age should be managed as above: GPP

Investigations including lumbar puncture, long bone X-rays, ophthalmology and audiology are recommended: GPP

Parents, siblings and any sexual partners may require screening for syphilis: GPP

Any child with a penicillin allergy should undergo desensitisation and then receive treatment with penicillin: GPP

The recommended treatment is benzyl penicillin 25 mg/kg (maximum 2.4 g) 6 hourly for 10 days: GPP

Ceftriaxone 100 mg/kg (maximum 4 g) once daily is recommended for ambulatory care for 10–14 days, if hospital admission is not possible: GPP.

Follow-up. Passively transferred maternal non-treponemal (RPR) antibody levels are expected to decline by 3 months of age and disappear by 6 months.

Infants born to people diagnosed and/or treated for syphilis during the present pregnancy require treponemal and non-treponemal tests including IgM test at birth and at 3 months of age. The RPR should be tested 3 monthly until negative. If these titres remain stable or increase, the child should undergo investigations as above for high-risk

Table 5. Investigations for infants at high risk of congenital syphilis.

Any lesions	Direct demonstration of *T. pallidum* by dark ground microscopy and/or PCR[61] of exudates or body fluids e.g. nasal discharge
Blood tests	Paired serological tests should be performed on the mother or pregnant person and infant. Perform treponemal and quantitative non-treponemal tests using infant's blood (not cord blood). Serological tests detecting IgG may be positive due to passive transfer of maternal antibodies whether or not the infant is infected
The following results indicate a diagnosis of congenital infection	
• Demonstration of *T. pallidum* by positive PCR or dark ground microscopy	
• Positive IgM EIA test (confirm on a repeat test[62])	
• Positive RPR test on cerebrospinal fluid (CSF)[50]	
• A ≥4-fold difference in RPR greater than that of the mother	
• A ≥4-fold increase in RPR titre within 3 months of birth	
• In a child more than 12–18 months age, any positive treponemal tests	
If a mother or pregnant person acquires syphilis and seroconverts late in pregnancy the baby may be delivered, and possibly infected, prior to a mature antibody response.In addition, an unwell baby may receive empirical antibiotics for sepsis which may attenuate the antibody response. This results in a low RPR titre and negative IgM, even in the presence of congenital infection.	
Further investigations of particular importance in symptomatic infants	
• Blood: full blood count, blood film, liver function, electrolytes, creatinine, lactate, bone chemistry	
• Consider testing for other congenital 'SCORTCH' infections[33] such as HIV, hepatitis and herpes simplex virus	
• CSF[51]: Cells, protein, RPR	
• Urine: Test for blood/protein	
• X-rays of long bones	
• Ophthalmic assessment	
• Audiology	

Table 6. Treatment of congenital syphilis.

Benzylpenicillin[63–71]	25 mg/kg (maximum 2.4 g)[72,73] IV for 10 days	
	Neonate up to 7 days[74]	12 hourly[75]
	Neonate 7–28 days	8 hourly
	Term >28 days	6 hourly
Ceftriaxone	<1 year old	75 mg/kg OD IV for 10 days
	>1 year old	100 mg OD IV for 10 days

OD: once daily; IV: intravenous.

congenital syphilis, including lumbar puncture, and treated for congenital syphilis.

It is not necessary to repeat treponemal tests every 3 months until negative.

Infants treated for congenital syphilis at birth should have an RPR test at birth and at 3, 6 and 12 months. The infant may be discharged at this time if a sustained 4-fold drop in RPR titre has been achieved from the peak level or is negative. Treponemal tests are likely to remain positive long term in the infant who has had congenital syphilis, but the titre usually falls over the first 12 months after birth.

Infants with evidence of neurosyphilis. If there is evidence of neurosyphilis in the infant, the following is recommended:

- In infants where the CSF RPR is positive, or the CSF protein level is elevated, repeat lumbar puncture at 6-monthly intervals until CSF RPR is negative and CSF protein is in the normal range.
- If CSF RPR is unchanged or increased, repeat treatment.[51]

Notification. ISOSS should be notified of all positive antenatal screening treponemal serology results and all infants infected with syphilis.[52]

Each maternity unit should register one or more neonatal or paediatric respondent(s) who will be sent a link to follow in order to complete the outcome for the infant. ISOSS should also be notified about children with syphilis, where the mother was not diagnosed in pregnancy.

Infant feeding. Treated maternal syphilis is not a contraindication to breastfeeding. A mother with active syphilitic lesions on the breasts should avoid breastfeeding until these have been effectively treated.

Auditable outcomes. The percentage of confirmed syphilis cases having a record of an RPR titre obtained at treatment (standard 97% of confirmed syphilis cases).

The percentage of confirmed syphilis cases having fully adhered to a recommended treatment (standard 97% of confirmed syphilis cases).

The percentage of cases having the outcome of (an) agreed contact action(s), or the decision not to contact, documented for all contacts, within the appropriate look back interval (see https://www.bashh.org/resources/100/2012_bashh_statement_on_partner_notification_for_sexually_transmissible_infections) (standard 97% of confirmed syphilis cases).

The percentage of pregnant women and people with a birth plan in place at the time of delivery (standard 97% of cases).

The percentage of infants receiving appropriate follow-up according to the birth plan at 6 months following birth (target 90% of cases).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Margaret Kingston https://orcid.org/0000-0001-5792-8529
Janet Wilson https://orcid.org/0000-0001-9865-0834

Supplemental Material

Supplemental material for this article is available online.

References

1. British Association for Sexual Health and HIV. 2015 framework for guideline development and assessment (2019 update), https://www.bashhguidelines.org/media/1229/2015-guidelines-framework-amended-dec-2019.pdf (2019, accessed 7th December 2022).
2. Ricci JM, Fojaco RM and O'Sullivan MJ. Congenital syphilis: the University of Miami/Jackson Memorial Medical Center experience, 1986-1988. *Obstet Gynecol* 1989; 74: 687–693.
3. Sheffield JS, Sánchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. *Am J Obstet Gynecol* 2002; 186: 569–573.
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.
5. Braccio S, Sharland M and Ladhani SN. Prevention and treatment of mother-to-child transmission of syphilis. *Curr Opin Infect Dis* 2016; 29: 268–274.
6. Public Health England. Antenatal screening standards: data report 1 April 2019 to 31 March 2020 (tables 28 and 31), https://www.gov.uk/government/statistics/antenatal-screening-standards-data-report-2019-to-2020/antenatal-screening-standards-data-report-1-april-2019-to-31-march-2020 (2021, accessed 18th November 2022).
7. Public Health England. ISOSS congenital syphilis case review report: 2015 to 2020. https://www.gov.uk/government/publications/integrated-screening-outcomes-surveillance-service-isoss-annual-report/isoss-congenital-syphilis-case-review-report-2015-to-2020 (2021, accessed 18th November 2022).
8. Simms I, Tookey PA, Goh BT, et al. The incidence of congenital syphilis in the United Kingdom: February 2010 to January 2015. *BJOG* 2017; 124: 72–77.
9. NHS England. NHS infectious diseases in pregnancy screening (IDPS) programme: detailed information, https://www.gov.uk/topic/population-screening-programmes/infectious-diseases-in-pregnancy (accessed 18th November 2022).
10. NHS England. Screening tests for you and your baby. *Infectious diseases* 2022. https://www.gov.uk/government/publications/screening-tests-for-you-and-your-baby/infectious-diseases (accessed 18th November 2022).
11. Public Health England. Infectious disease in pregnancy screening programme. handbook: https://www.gov.uk/government/publications/infectious-diseases-in-pregnancy-screening-programme-handbook (2016, accessed 18th November 2022).
12. NHS England. Infectious disease in pregnancy screening programme: laboratory handbook. https://www.gov.uk/government/publications/infectious-diseases-in-pregnancy-screening-programme-laboratory-handbook (2022, accessed 18th November 2022).
13. NHS Health Education England. e-learning for healthcare. https://www.e-lfh.org.uk/ (2023, accessed 10th February 2023).
14. Harter C and Benirschke K. Fetal syphilis in the first trimester. *Am J Obstet Gynecol* 1976; 124: 705–711.
15. NHS England. ISOSS syphilis report 2022. https://www.gov.uk/government/publications/infectious-diseases-in-pregnancy-screening-isoss-syphilis-report-2022/isoss-syphilis-report-2022 (2022, accessed 9th February 2023).
16. Kingston M, Apea V, Evans C, et al. BASHH guidelines for the management of syphilis. *International Journal STD & AIDS*. 2024.
17. Wendel GD, Sheffield JS, Hollier LM, et al. Treatment of syphilis in pregnancy and prevention of congenital syphilis. *Clin Infect Dis* 2002; 35(2): S200–S209.
18. Zhu L, Qin M, Du L, et al. Maternal and congenital syphilis in Shanghai, China, 2002 to 2006. *Int J Infect Dis* 2010; 14(3): e45–e48.
19. Hawkes S, Matin N, Broutet N, et al. Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. *Lancet Infect Dis* 2011; 11: 684–691.
20. Hollier LM, Harstad TW, Sanchez PJ, et al. Fetal syphilis: clinical and laboratory characteristics. *Obstet Gynecol* 2001; 97: 947–953.
21. Nathan L, Bawdon RE, Sidawi JE, et al. Penicillin levels following the administration of benzathine penicillin G in pregnancy. *Obstet Gynecol* 1993; 82: 338–342.
22. Zhou P, Gu Z, Xu J, et al. A study evaluating ceftriaxone as a treatment agent for primary and secondary syphilis in pregnancy. *Sex Transm Dis* 2005; 32: 495–498.
23. Roberts CP, Raich A, Stafylis C, et al. Alternative treatments for syphilis during pregnancy. *Sex Transm Dis* 2019; 46: 637–640.

24. Klein VR, Cox SM, Mitchell MD, et al. The JarischHerxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol* 1990; 75: 375–380.
25. Myles TD, Elam G, Park-Hwang E, et al. The JarischHerxheimer reaction and fetal monitoring changes in pregnant women treated for syphilis. *Obstet Gynecol* 1998; 92: 859–864.
26. Poliquin V, Dhaliwal A, Lopez A, et al. Local rate of Jarisch-Herxheimer reaction following penicillin treatment for syphilis during pregnancy. *J Obstet Gynaecol Can* 2020; 42: 689.
27. Chakraborty R and Luck S. Syphilis is on the increase: the implications for child health. *Arch Dis Child* 2008; 93: 105–109.
28. World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis). https://www.who.int/publications/i/item/9789241549714 (2016, accessed 9th February 2023).
29. Janier M, Unemo M, Dupin N, et al. 2020 European guideline on the management of syphilis. *J Eur Acad Dermatol Venereol* 2021; 35: 574–588.
30. Workowski KA and Bolan GACenters for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep (Morb Mortal Wkly Rep)* 2015; 64: 1–137.
31. Lago EG, Vaccari A and Fiori RM. Clinical features and follow-up of congenital syphilis. *Sex Transm Dis* 2013; 40: 85–94.
32. Prochazka M, Evans J, Thorn L, et al. *Tracking the syphilis epidemic in England: 2010 to 2019*. London: Public Health England, 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/956716/Syphilis_Action_Plan_Metrics_2010_to_2019_report.pdf (accessed 9th February 2023).
33. Penner J, Hernstadt H, Burns JE, et al. Stop, think SCORTCH: rethinking the traditional 'TORCH' screen in an era of re-emerging syphilis. *Arch Dis Child* 2021; 106: 117–124.
34. Theel ES, Katz SS and Pillay A. Molecular and direct detection tests for treponema pallidum subspecies pallidum: a review of the literature, 1964–2017. *Clin Infect Dis* 2020; 71(1): S4–S12.
35. Garel B, Grange P, Benhaddou N, et al. Congenital syphilis: a prospective study of 22 cases diagnosed by PCR. *Ann Dermatol Venereol* 2019; 146: 696–703.
36. Cooper JM and Sanchez PJ. Congenital syphilis. *Semin Perinatol* 2018; 42: 176–184.
37. Porter S, Qureshi R and Benenson I. Understanding congenital syphilis. *Infants Young Child* 2018; 31: 287–296. https://journals.lww.com/iycjournal/Abstract/2018/10000/Understanding_Congenital_Syphilis.4.aspx
38. Kelly M, Hendry S and Norton R. The utility of the syphilis enzyme immunoassay IgM in the diagnosis of congenital syphilis. *Diagn Microbiol Infect Dis* 2020; 98: 115152.
39. Eagle H. Speculations as to the therapeutic significance of the penicillin blood level. *Ann Intern Med* 1948; 28: 260–278.
40. Liu HY, Han Y, Chen XS, et al. Comparison of efficacy of treatments for early syphilis: a systematic review and network meta-analysis of randomized controlled trials and observational studies. *PLoS One* 2017; 12: e0180001.
41. Liang Z, Chen YP, Yang CS, et al. Meta-analysis of ceftriaxone compared with penicillin for the treatment of syphilis. *Int J Antimicrob Agents* 2016; 47: 6–11.
42. Psomas KC, Brun M, Causse A, et al. Efficacy of ceftriaxone and doxycycline in the treatment of early syphilis. *Med Maladies Infect* 2012; 42: 15–19.
43. Spornraft-Ragaller P, Abraham S, Lueck C, et al. Response of HIV-infected patients with syphilis to therapy with penicillin or intravenous ceftriaxone. *Eur J Med Res* 2011; 16: 47–51.
44. Potthoff A and Brockmeyer N. Randomized, prospective, open-label study to compare the efficacy of treatment with benzathine penicillin or ceftriaxone in early syphilis in HIV-infected patients. *HIV Med* 2009; 10.
45. Schofer H, Vogt HJ and Milbradt R. Ceftriaxone for the treatment of primary and secondary syphilis. *Chemotherapy* 1989; 35: 140–145.
46. Moorthy TT, Lee CT, Lim KB, et al. Ceftriaxone for treatment of primary syphilis in men: a preliminary study. *Sex Transm Dis* 1987; 14: 116–118.
47. Katanami Y, Hashimoto T, Takaya S, et al. Amoxicillin and ceftriaxone as treatment alternatives to penicillin for maternal syphilis. *Emerg Infect Dis* 2017; 23: 827–829.
48. Marra CM, Boutin P, McArthur JC, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. *Clin Infect Dis* 2000; 30: 540–544.
49. Sobel J. Antenatal and neonatal protection of the infant. *Arch Pediatr* 1926; 43: 448–465.
50. Michelow IC, Wendel GD, Jr, Norgard MV, et al. Central nervous system infection in congenital syphilis. *N Engl J Med* 2002; 346: 1792–1798.
51. McCracken GH, Jr and Kaplan JM. Penicillin treatment for congenital syphilis. A critical reappraisal. *JAMA* 1974; 228: 855–858.
52. Public Health England. Infectious diseases in pregnancy screening programme: ISOSS. https://www.gov.uk/government/publications/integrated-screening-outcomes-surveillance-service-isoss/infectious-diseases-in-pregnancy-screening-programme-isoss (2019, accessed 9th February 2023).
53. Gomez GB, Kamb ML, Newman LM, et al. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ* 2013; 91: 217–226.
54. Hira SK, Bhat GJ, Patel JB, et al. Early congenital syphilis: clinico-radiologic features in 202 patients. *Sex Transm Dis* 1985; 12: 177–183.
55. Brion LP, Manuli M, Rai B, et al. Long-bone radiographic abnormalities as a sign of active congenital syphilis in asymptomatic newborns. *Pediatrics* 1991; 88: 1037–1040.
56. Centers for Disease Control (CDC). Congenital syphilis definitions - revised January 2015. https://www.cdc.gov/std/stats/congenitalsyphilisdef-rev-jan-2015.pdf (2015, accessed 9th February 2023).
57. Uchiyama K, Tsuchihara K, Horimoto T, et al. Phthisis bulbi caused by late congenital syphilis untreated until adulthood. *Am J Ophthalmol* 2005; 139: 545–547.
58. Stoll BJ. Congenital syphilis: evaluation and management of neonates born to mothers with reactive serologic tests for syphilis. *Pediatr Infect Dis J* 1994; 13: 845–852.
59. American Academy of Pediatrics. *Red book: report of committee on infectious diseases 23rd*. A AC02279603 - American Acad. of Pediatrics, 1994, pp. 445–455.

60. Liu JB, Hong FC, Pan P, et al. A risk model for congenital syphilis in infants born to mothers with syphilis treated in gestation: a prospective cohort study. *Sex Transm Infect* 2010; 86: 292–296.
61. Leslie DE, Azzato F, Karapanagiotidis T, et al. Development of a real-time PCR assay to detect Treponema pallidum in clinical specimens and assessment of the assay's performance by comparison with serological testing. *J Clin Microbiol* 2007; 45: 93–96.
62. Chhabra RS, Brion LP, Castro M, et al. Comparison of maternal sera, cord blood, and neonatal sera for detecting presumptive congenital syphilis: relationship with maternal treatment. *Pediatrics* 1993; 91: 88–91.
63. Hardy JB, Hardy PH, Oppenheimer EH, et al. Failure of penicillin in a newborn with congenital syphilis. *JAMA* 1970; 212: 1345–1349.
64. Thomas EW. Rapid treatment of syphilis with penicillin; a survey of the problem. *Bull World Health Organ* 1949; 2: 233–248.
65. Thomas EW. Rapid treatment of syphilis with penicillin; penicillin in prenatal and infantile syphilis. *Bull World Health Organ* 1949; 2: 249–255.
66. Zenker PN and Rolfs RT. Treatment of syphilis, 1989. *Rev Infect Dis* 1990; 12(6): S590–S609.
67. Platou RV and Hill AJ, Jr. Penicillin in the treatment of infantile congenital syphilis: a brief preliminary note. *JAMA* 1945; 127: 582.
68. Platou RV, Hill AJ, Jr and Ingraham NR. Effect of penicillin in the treatment of infantile congenital syphilis; further observations. *Am J Dis Child* 1946; 72(6): 635–648.
69. Platou RV, Hill AJ and Ingraham NR. Early congenital syphilis; treatment of two hundred and fifty-two patients with penicillin. *J Am Med Assoc* 1947; 133: 10–16.
70. Rose EK, Gyorgy P and Ingraham NR, Jr. Treatment of infantile congenital syphilis; results with aqueous penicillin alone in 60 infants followed for an average of 2 years after treatment. *Am J Dis Child* 1949; 77: 729–735.
71. Barker LP. An evaluation of the penicillin treatment in early congenital syphilis. *J Pediatr* 1948; 32: 516–521.
72. Azimi PH, Janner D, Berne P, et al. Concentrations of procaine and aqueous penicillin in the cerebrospinal fluid of infants treated for congenital syphilis. *J Pediatr* 1994; 124: 649–653.
73. Idsoe O, Guthe T and Willcox RR. Penicillin in the treatment of syphilis. The experience of three decades. *Bull World Health Organ* 1972; 47: 1–68.
74. Bernard B, Linsley L and Mapp J. 231 Pharmacokinetics of aqueous penicillins in cerebrospinal fluid of neonates. *Pediatr Res* 1978; 12: 402.
75. Padari H, Metsvaht T, Germovsek E, et al. Pharmacokinetics of penicillin G in preterm and term neonates. *Antimicrob Agents Chemother* 2018; 62: e02238.17.