NZSHS
THE NEW ZEALAND SEXUAL HEALTH SOCIETY INCORPORATED
SEXUAL HEALTH FOR ALL

Syphilis in Pregnancy

Antenatal Management Guidelines for maternal and congenital syphilis

Released 2020

Contents

1. Purpose and need for guideline

The purpose of this guideline is to provide a national guideline on the assessment, care, treatment and follow up of syphilis in pregnant women and neonates born to mothers with syphilis in pregnancy. The goal of this work, in conjunction with other parts of the National Syphilis Action Plan 2019 (NSAP) is to reduce morbidity and mortality from syphilis in pregnancy, and ultimately eliminate congenital syphilis in New Zealand. Guidelines for syphilis screening in pregnancy will be published separately.

There is an urgent need for this guideline because untreated syphilis has serious and potentially fatal consequences for mothers and babies, and there has been a rapid rise in syphilis cases among women in recent years with a corresponding increase in cases of congenital syphilis including stillbirths. Incorrect or delayed management or inadequate follow up can result in increased morbidity. Development and use of national best practice guidelines will optimise management of syphilis in pregnancy and the neonatal period, and facilitate the development of regional guidelines. Each region will also need to identify a referral pathway for affected pregnancies.

2. Intended users

This guideline is intended as a reference for all clinicians involved in the care of pregnant women and neonates. This includes:

- Obstetricians and trainees and midwives and midwifery undergraduate students.
- Neonatologists, Paediatricians and trainees.
- Infectious Diseases Physicians and trainees.
- Sexual Health Physicians and trainees.
- General Practitioners, trainees, and the wider primary care team.

3. Te Tiritiri o Waitangi

The New Zealand Sexual Health Society (NZSHS) and the Ministry of Health recognise and affirm the right of Māori to equitable health outcomes as underpinned by Te Tiritiri o Waitangi. Of particular concern relating to this clinical guideline is the disproportionate burden of congenital syphilis suffered by Māori. The availability of best practice guidelines for assessment, care, treatment and follow up are intended to support the effective management of families affected by syphilis, but a much broader response will be required to eliminate inequities for Māori. This includes but is not limited to the provision and resourcing of options such as Kaupapa Māori services and whānau centred services alongside culturally safe mainstream

health services; specific allocation of resource and effort to eliminating inequity by building the Māori health workforce and eliminating racism; and ensuring the ongoing collection and dissemination of robust information on Māori health outcomes.

4. Guideline Development process

A dedicated core National Syphilis in Pregnancy guideline group was established by NZSHS, comprised of sexual health physicians. A draft guideline was developed by this group based on review of international guidelines and literature. Electronic and telephone consultation was then undertaken with the national NZ sexual health physician peer group, followed by representatives from the following specialties and organisations; infectious diseases, microbiology, obstetrics and gynaecology, paediatric infectious diseases, neonatology, midwifery (NZ College of Midwives and Nga Maia Māori Midwives Aotearoa), the Royal New Zealand College of General Practitioners, public health medicine and Te Whāriki Takapou. A final draft was circulated with responses to feedback received. The draft guideline was also discussed at the National Syphilis Action Plan planning day on 27th September 2019, and the NZSHS annual conference on 15th November 2019.

Guidelines for syphilis screening in pregnancy beyond the established first antenatal screen will be developed by the Ministry of Health maternity group and published separately.

Core NZSHS guideline group members

Dr Teena Mathew (lead author, sexual health physician)

Dr Jane Morgan (sexual health physician)

Dr Jane Kennedy (sexual health physician)

Dr Julia Scott (President, NZSHS)

External reviewers

Primary care

Dr Sue Tutty (RNZCGP)

Obstetrics and Gynaecology

Prof Peter Stone

Dr Celia Devenish (RANZCOG)

Dr Kate Coffey (RANZCOG)

Dr Emma Deverall

Neonatology

Dr David Hou

Dr Michael Meyer

Paediatric Infectious Diseases

Dr Emma Best

Dr Rachel Webb

General Paediatrician

Dr Nicola Pereira

Microbiology

Dr Arlo Upton

Dr Gary McAuliffe

Public Health Medicine

Dr Catherine Jackson

Dr Subha Rajanaidu

Midwifery

Dr Lesley Dixon, Midwifery advisor for the New Zealand College of Midwives

Adrienne Priday, Co-chair of the Auckland region for the New Zealand College of Midwives, practising midwife, and educator (AUT)

Nga Maia Māori Midwives Aotearoa

Infectious diseases

Dr Massimo Giola

Sexual Health Physicians - RACP Peer Group

Paediatric Pharmacists

Laura Millward

Eamon Duffy

5. Funding of the guideline

This guideline was developed without dedicated funding. Core guideline group teleconference costs were covered by NZSHS, and consultation teleconferences were facilitated by the Ministry of Health. NZSHS members and external reviewers completed work on a voluntary basis.

6. Endorsements

TBC

7. Editorial independence

The NZSHS guideline group members have no conflicts of interest to declare.

8. Background

8.1 Epidemiology of congenital syphilis in NZ

Provisional 2018 data from ESR shows over 500 infectious syphilis cases were reported in New Zealand which is likely a significant under-estimation given surveillance limitations and undiagnosed infections. Most reported cases continue to affect men who have sex with men. However, there has been a notable and rapid rise in infectious syphilis amongst heterosexual men and women since 2015, particularly among Māori. Most of this increase is among women of reproductive age.

Hence, congenital syphilis infections, including neonatal deaths, have increased since 2016 after being incredibly rare for many years. Since 2016 fourteen cases of congenital syphilis having been reported including six stillbirths.[1] Case finding of syphilis in pregnancy through screening and testing and early treatment of these cases can prevent many of the consequences of congenital syphilis.

The recent increase of syphilis cases among heterosexuals is disproportionately among those with socioeconomic disadvantage and reflects a complex overlap of wider social determinants, structural issues and risky behaviour. Risk-taking behaviours, including substance use and high-risk sex, are predicted by adverse childhood and youth experiences including family and sexual violence.[2] Socio-economic adversity, substance abuse, incarceration, inadequate access to healthcare and lack of support are additional factors known to drive sexually transmitted infection (STI) outbreaks amongst more vulnerable communities.[3] Bisexual men can act as a bridge between heterosexuals and other close-knit risk groups like gay men.[4]

8.2 Natural history of infection with syphilis

Syphilis is caused by *Treponema pallidum pallidum,* a highly motile spiral-shaped Gram-negative bacterium. It is transmitted by direct contact with an infectious lesion or by vertical transmission (transplacental) during pregnancy. Syphilis is a multi-stage, multi-system disease, which is broadly defined as congenital or acquired.

Acquired syphilis can be divided into **primary** (ulcer or chancre stage), **secondary** (systemic dissemination), **early latent** (within 2 years of acquisition with no symptoms), **late latent** (> 2 years since acquisition with no symptoms) and **tertiary** syphilis (symptomatic late syphilis e.g. gummas, cardiovascular and neurological involvement).

Primary syphilis presents with an ulcer or chancre at the site of infection. The ulcer is usually painless with a well-defined edge and indurated base. Presentation is on average 3 weeks after acquisition (incubation period 10-90 days).

Secondary syphilis usually presents with constitutional symptoms such as fever, malaise, headache and lymphadenopathy. A rash often occurs typically involving the palms and soles but also may affect the trunk. There may be alopecia and condylomata lata (warty growths in the ano-genital area). There may also be neurological signs of cranial nerve palsies, ophthalmic signs and meningitis. Hepatitis may also be present. Presentation is on average 6 weeks after acquisition (range 2-24 weeks).

Tertiary syphilis occurs from one to many years after untreated infection. This may involve the brain and spinal cord (neurosyphilis), cardiovascular system or cause skin lesions (gummas). It is important to note neurosyphilis can occur at any stage of syphilis.

Latent syphilis is when a person tests positive for syphilis infection without any symptoms or signs of syphilis. Early latent syphilis is defined as positive syphilis serology with no symptoms and infection acquired within the last 2 years, usually evidenced by negative syphilis tests dated less than 2 years. Late latent syphilis is defined as positive syphilis serology with no symptoms and acquisition >2 years. If there is any doubt about the time of acquisition, the infection should be treated as late latent syphilis.

It is important to note that around 50% of patients with early syphilis report no symptoms.[16]

8.3 Syphilis in pregnancy

Pregnancy does not affect the clinical presentation of syphilis. However, syphilis infection can significantly affect the course of the pregnancy leading to adverse pregnancy outcomes (APO). APOs are at least 50% higher in untreated syphilis infections when compared to women with negative syphilis serology and include miscarriage, stillbirth, premature birth, neonatal death, low birth weight, small for size gestational age, and congenital syphilis in a live-born infant.[5,6]

Fetal infection results from haematogenous spread from an infected mother through the placenta. Rarely direct transmission is possible from an infected mother to her infant at the time of birth through infectious genital lesions.[7]

The risk of a baby being born with congenital syphilis is very high during the first 4 years after the woman first acquires syphilis and is negligible after she has been infected for over 8 years.

The risk of congenital syphilis is directly related to the stage of syphilis during pregnancy and the duration of exposure of the fetus. The risk of congenital infection and APOs for untreated pregnant women is 100% for primary syphilis and secondary syphilis, 80% for early latent and 10% for late latent syphilis.[8]

The risk of congenital syphilis in babies born to women treated during pregnancy is still between 1-2% and hence babies born to women treated for syphilis in current pregnancy require evaluation at birth.[9] Women with syphilis who received antenatal care in the first and second trimesters of pregnancy are more likely to give birth to a healthy infant.[10] Women

treated for syphilis in the third trimester have more APOs than women treated before 28 weeks gestation.[6]

Fetal abnormalities due to congenital syphilis are usually seen after 20 weeks of gestation when immune maturity occurs. It is the host immune response to the bacteria that causes the pathological changes.[11]

Ultrasound signs of congenital syphilis in the fetus, if present, are usually seen after 18-20 weeks gestation. They include hepatomegaly, placentomegaly, polyhydramnios, ascites and elevated middle cerebral artery peak systolic velocity.[12,13] Less frequent findings include bowel dilatation and long bone abnormalities.[13] Abnormal ultrasound findings prior to treatment is associated with treatment failure and delivery of a neonate with congenital syphilis.[12]

8.4 Syphilis infection in the new-born

8.4.1 Early congenital syphilis

Early congenital syphilis is defined as onset within the first 2 years of age. Most affected infants are asymptomatic at birth and usually develop clinical features within 3 months with most infants presenting within the first 5 weeks of life. The clinical and laboratory findings in congenital syphilis are varied and unpredictable and can mimic other neonatal conditions.[14]

The major clinical features of early congenital syphilis in decreasing frequency of occurrences are:

Features of early congenital syphilis
Hepatomegaly with or without splenomegaly
Radiographic bone changes (periostitis; osteochondritis); pseudoparalysis of Parrot
Lymphadenopathy
Jaundice
Rash
Hepatitis (elevated transaminase concentrations)
Anemia and/or thrombocytopenia
Respiratory distress (pneumonia)
Fever

Features of early congenital syphilis
Small for gestational age; Birth weight <2500gm
Failure to thrive or slow weight gain
Nonimmune hydrops
Rhinitis, mucous patch, condyloma lata, nephrotic syndrome, myocarditis, diarrhoea (malabsorption), pancreatitis, chorioretinitis, cataract
Central nervous system (leptomeningitis, cranial nerve palsies, cerebral infarction, seizures, hypopituitarism)
(Table adapted from Cherry's Textbook of Pediatric Infectious Diseases[14] and Avery's Diseases of the Newborn & Feigin[29])

8.4.2 Late congenital syphilis

Untreated or inadequately treated cases of early congenital syphilis may develop late congenital syphilis, which is analogous to tertiary syphilis in adults. Late congenital syphilis is usually diagnosed in late childhood or early adolescence.

The major clinical features of late congenital syphilis are:[14]

- Deformation of bones *(Frontal boss of Parrott, short maxilla, high palatal arch, Higouménakis sign, relative protuberance of mandible, saddle nose, Saber shin, scaphoid scapulae, Clutton joint)*
- Deformation of teeth *(Mulberry molars, Hutchinson teeth)*
- Interstitial keratitis of the eyes causing photophobia, pain and blurred vision
- Neurosyphilis causing behavioural disturbance, ataxia and cranial neuropathies
- Sensorineural hearing loss.

9. Diagnostics

In New Zealand, syphilis serology is the diagnostic test of choice. There are 2 types of standard serology tests; treponemal and non-treponemal.

A Treponemal test (EIA-Enzyme Immunoassay Assay) is used as the initial screening test in New Zealand. All reactive EIA tests will be reflex-tested with a second treponemal test (TPPA - Treponema pallidum particle agglutination) and a non-treponemal test (RPR - Rapid Plasma Reagin). If the TPPA is also reactive then current or past syphilis infection is confirmed. The RPR

is less specific but if reactive provides a quantitative result that correlates with disease activity and can be used to monitor adequacy of treatment. VDRL (Venereal Disease Research Laboratory) is the preferred non-treponemal test on cerebrospinal fluid (CSF).

There are also tests available for direct identification of the organism from lesions (e.g. dark field microscopy, direct fluorescent antigen (DFA) testing and nucleic acid amplification tests (NAAT e.g. polymerase chain reaction PCR). These are only available in select laboratories in New Zealand with restricted access to the tests. These tests are useful in supporting the diagnosis of congenital syphilis and primary or secondary syphilis.

9.1 Interpretation of syphilis serology in adults

Interpretation of syphilis serology can be difficult and therefore cases should always be discussed with a specialist (sexual health physician or infectious diseases physician) with expertise in diagnosing syphilis.

Table 1

EIA	TPPA	RPR	Interpretation
Reactive	Reactive	Reactive	Confirmed syphilis infection
Reactive	Reactive	Non-reactive	Evidence of past treated syphilis or latent infection OR very early infection,
Reactive	Non- reactive	Reactive	Biological false positive OR very early infection Repeat in 2 weeks
Reactive	Non-reactive	Non-reactive	Possible early primary, latent or false-positive, retest in one month
Non - reactive	Not tested	Not tested	No evidence of syphilis, or too early, retest in one month if strong suspicion based on clinical evidence.

Adapted from BPAC[30]

Syphilis serology can be negative in the primary stage of syphilis (chancre or ulcers). In these cases, specialist clinics usually have access to DFA or *Treponema pallidum* NAAT testing and so early referral to a sexual health clinic is recommended. Repeat serology two weeks after the initial tests in the presence of a chancre, usually yields a reactive test result. Serology is reactive in nearly all cases of secondary syphilis.

A 2-titre or 4-fold rise of non-treponemal test titre (RPR) following a previous result indicates a new infection. A 2-titre or 4-fold decline after treatment indicates an adequate response to treatment. For example, a decrease of RPR titres after treatment from 1:16 to 1:4 is indicative of adequate treatment. Conversely for example, a rise in RPR titres after treatment from 1:2 to 1:8 is indicative of re-infection or treatment failure.

Adults with reactive treponemal tests (TPPA/EIA) will usually stay reactive for life even after treatment. Non-treponemal tests such as RPR may become non-reactive after treatment and in approximately 25% of cases of late latent syphilis RPR seroreversion can occur without

treatment. Therefore, a non-reactive RPR does not necessarily indicate a previously treated infection.

9.2 Interpretation of syphilis serology in new-borns

The interpretation of syphilis serology in neonates requires specialist input as no single test can be used to diagnose congenital syphilis. Passive transfer of maternal antibodies makes interpretation of neonate serology more complex.

A non-treponemal test titre (e.g. RPR), which is 4-fold (or 2 dilution) higher than the maternal RPR at birth is indicative of fetal antibody synthesis and is consistent with congenital syphilis. For example, if the mother's RPR at delivery is 1:4 and infant's serology at birth has RPR of 1:16, then this is consistent with a diagnosis of congenital syphilis.

Elevated/positive maternal RPR at birth and any elevation of neonatal RPR above maternal level may be suggestive of congenital syphilis and/or maternal/fetal treatment failure and thus needs consideration of treatment and discussion with paediatric infectious diseases team (refer to neonatal management, Section 11.1).

The diagnosis of congenital syphilis in an untreated infant can be excluded if non- treponemal tests (e.g. RPR or VDRL) become non-reactive before 6 months of age.[15]

Treponemal tests like TPPA demonstrate IgG, IgA and IgM antibodies to *Treponema pallidum* but do not differentiate between them. Therefore, a reactive TPPA test in a neonate could be passively transferred IgG component of TPPA and not necessarily an infected baby.[15] This can persist in an infant until 15 months of age. However, a treponemal test that remains reactive from birth to after 18 months of age is diagnostic of congenital syphilis.[17]

IgM treponemal tests can be used to differentiate between passively transferred antibodies and fetal antibody production in response to infection.[15] This test is available through very limited laboratories in New Zealand. A negative IgM result however cannot exclude congenital syphilis. Issues with false positives and false negative tests are not uncommon with IgM tests.

A reactive IgM test, in the absence of other indicators for congenital syphilis warrants consideration of treatment and discussion with Paediatric Infectious Diseases Team.

10. Management of women with positive syphilis serology during pregnancy

1. Refer all reactive syphilis serology in pregnancy to a clinician with expertise in managing syphilis (see Appendix 2 - flowchart). This will typically be an urgent referral pathway to the local Sexual Health Service or Infectious Diseases Service. Clinicians who do not manage syphilis infection on a regular basis should be not be expected to give advice or manage syphilis in pregnancy.

2. The treating clinician service is responsible for undertaking ESR notification and contact tracing. Midwives and other primary maternity service practitioners who order syphilis screening as part of pregnancy care, are not expected to complete the ESR notification for positive results but are expected to refer to a specialist service.
3. All DHBs need to have a clear local pathway for referrals from Lead Maternity Carers (LMC) and other health professionals for management of reactive syphilis serology in a pregnant woman.[25]
4. DHBs should identify named clinicians who will be responsible for the care of the woman, her sexual contacts and her new-born with respect to management of syphilis in pregnancy.
5. All attempts should be made to treat a pregnant woman with syphilis before the latter half of her pregnancy for the best possible outcome for her pregnancy.
6. Offer a full STI screen including gonorrhoea, chlamydia, trichomoniasis and serology for HIV to all women with a positive syphilis serology result.
7. Clinical records and letters should clearly indicate which clinician is responsible for management decisions of the mother and the neonate and which service is responsible for serological follow up of the mother and neonate.
8. A successful outcome requires a co-ordinated multidisciplinary approach involving midwives, Sexual Health or Infectious Diseases Physicians, Sexual health nurses, contact tracers (Public health), Obstetricians, Paediatric and Neonatal teams, Primary Care teams' social workers, community care workers and Plunket nurses.

10.1 Assessment and staging

Assess women with reactive syphilis serology thoroughly for signs and symptoms of syphilis. Obtain a detailed sexual history, previous syphilis test results or past syphilis diagnosis with treatment details and subsequent test results.

Based on the above information, a clinician with expertise in managing syphilis will usually be able to identify the stage of the infection and determine the appropriate management and treatment. In cases where it is not clear then it is recommended the patient be given a full course of treatment as for late latent syphilis.

Offer all women with reactive serology a full STI screening including testing for gonorrhoea, chlamydia, trichomoniasis and serology for HIV.[21]

10.2 Treatment

Treatment should be appropriate for the stage of disease (primary, secondary, early or late latent, tertiary or neurosyphilis) and should be discussed with a sexual health physician or infectious diseases physician as per local DHB referral pathway.

Parenteral penicillin is the recommended treatment for syphilis in pregnancy as given below.[18,19,20,21,22]

It is also important to repeat syphilis serology on the day of treatment to accurately document the pre-treatment RPR titre but DO NOT DELAY treatment whilst arranging this.

10.2.1 Early syphilis in pregnancy (primary, secondary, early latent but excluding neurosyphilis)

- Trimester 1 or 2 (up to and including 27 weeks):
    - Benzathine benzylpenicillin tetrahydrate 2,400,000 units/4.6 ml intramuscularly as a **single dose**

- Trimester 3 (from week 28 to term):
    - Benzathine benzylpenicillin tetrahydrate 2,400,000 units/4.6 ml intramuscularly, on days 1 and 8 (**2 doses**)

NB Ensure correct form of parenteral penicillin is prescribed and administered. Benzathine benzylpenicillin tetrahydrate is a long-acting injection intended for intramuscular use. Benzylpenicillin is intended for intravenous use.

There are no randomised controlled studies looking at the efficacy of one dose over two doses of benzathine benzylpenicillin in third trimester. However, there are studies which show decreased penicillin concentrations in the third trimester due to physiological changes in pregnancy.[23] Also, treatment is less effective at preventing congenital transmission if given in the third trimester, especially within 4 weeks of birth.[6,9,10,24] For this reason, a second dose of benzathine benzylpenicillin tetrahydrate, a week after the first dose, is recommended in treatment of early syphilis in the third trimester.[12,22]

Benzathine benzylpenicillin tetrahydrate is available in a pre-filled syringe containing 1,200,000 units/2.3mL. Doses recommended above are usually administered as 1,200,000 units/2.3mL into ***each*** *buttock i.e. 2 separate injections.*

10.2.2 Late syphilis in pregnancy and syphilis of unknown duration (all three trimesters)

- Benzathine benzylpenicillin tetrahydrate 2,400,000 units/4.6 ml weekly on days 1, 8 and 15 (**three doses**).
- If there is any doubt about the time of acquisition in latent disease, it should be treated as late latent syphilis.
- ***Missed doses –*** it is really important that the full prescribed course of treatment is provided for all pregnant women. If a dose is missed during the treatment of late latent syphilis in pregnancy, then the full course will need to be repeated.[31] If in doubt, please discuss with a physician with expertise in managing syphilis in pregnancy.

10.2.3 Neurosyphilis (all trimesters)

- Assess pregnant women with positive syphilis serology and neurological, ocular or otologic symptoms for signs and symptoms of neurosyphilis. The National Syphilis

Action Plan requires each DHB to put management pathways in place for complicated syphilis such as neurosyphilis.[25] This usually involves an urgent referral to an infectious diseases physician/general medical physician (as per local DHB pathway) for possible lumbar puncture and further management based on these results.

- If neurosyphilis is confirmed, treat as per neurosyphilis treatment regimen[20,22] with:
  - **Benzylpenicillin sodium (Penicillin G),** 1.8g – 2.4 g IV every 4 hours **OR** 10.8g – 14.4g as a continuous IV infusion over 24 hours via an outpatient parental antibiotic service (if suitable) for 10-14 days.

  (Continuous infusion needs to be prepared as a buffered solution - consult local pharmacy for advice).

10.3 Special considerations

10.3.1 Syphilis infection treated prior to pregnancy

Women previously treated adequately for syphilis do not require further treatment or assessment for themselves or the neonate if **ALL** the following conditions are met:

1) Treatment with a penicillin or doxycycline regimen was adequate for their stage of infection prior to current pregnancy.
2) The treatment given can be verified from clinical records or letters; verbal self-reports of treatment should not be taken as confirmation of adequate treatment for the stage of syphilis.
3) Treatment was completed before current pregnancy.
4) There is a documented adequate serological response (4-fold or two dilution drop in RPR) and if serofast, that the level is consistently stable with RPR ≤1:4.
5) There is no clinical suspicion of syphilis infection during current pregnancy.

(Adapted from Clement et al,[17] CDC syphilis guidelines,[20] and Northern territory syphilis guidlines[26])

If in doubt, discuss with a sexual health physician or infectious diseases physician.

10.3.2 Penicillin allergy

- Penicillin is the only drug that is recommended for treatment of syphilis in pregnancy. The evidence for using ceftriaxone or amoxicillin in pregnancy is limited and is therefore not recommended.[27] Doxycycline is contraindicated in pregnancy. Treatment with macrolides is not recommended as they do not reliably cross the placenta. There are also increasing reports of macrolide resistance in different geographical regions including Australia.
- Therefore, any woman with penicillin allergy should be admitted to hospital for de-sensitisation.

- Discuss with an immunologist or allergy specialist regarding allergy assessment and desensitisation.
- Centres for Disease Control and Prevention (CDC) gives some guidance on *Management of Persons Who Have a History of Penicillin Allergy* on their website.

10.3.3 Syphilis diagnosis > 20 weeks of pregnancy

- It is important to **involve the obstetric team** early, especially if treatment is initiated in the second half of pregnancy.
- A fetal ultrasound is recommended in women over 20 weeks of gestation.[20] Ultrasound abnormalities if present, indicate a greater risk for treatment failure and also the likelihood of fetal compromise during treatment due to Jarisch-Herxheimer reaction (see Section 10.3.4).[12]
- The local obstetric team should facilitate admission for administration of the first dose of benzathine benzylpenicillin tetrahydrate injection in these women.
- It is important to remember that a normal pre-treatment ultrasound does not rule out congenital infection. **Do not delay treatment if there is any delay in arranging an ultrasound.**

10.3.4 Jarisch-Herxheimer (JH) reaction

- This is an acute febrile illness associated with headaches, myalgia, arthralgia, chills, rigors and pharyngitis. These symptoms usually occur 2-8 hours after treatment for syphilis is initiated and resolve within 24 hours. This is common in early syphilis and is usually not clinically significant unless there is neurological or ophthalmic involvement or in pregnancy.
- JH reaction occurs in up to 44% of pregnant women and can precipitate preterm labour, and fetal heart rate abnormalities. Stillbirth is a very rare complication of treatment, (usually in case of severely affected fetuses),[12] but concern for this possible complication should not delay treatment.
- All viable pregnancies (≥20 weeks gestation) must be treated in association with the local obstetric team. Treatment should be given without delay however the woman should be advised that as a reaction to the first dose of treatment may occur, a short period of admission is recommended for continuous fetal monitoring. This may be between 8 -24 hours.[12] The remaining doses may be given as an outpatient. If the JH reaction induces preterm labour, management should follow standard obstetric care. In some cases where the woman declines admission, it is acceptable to advise the woman to seek obstetric attention after treatment if they notice any fever, contractions, or decrease in fetal movements.[20]

10.3.5 HIV positive pregnant woman with syphilis

- All women with HIV infection should be tested for syphilis during antenatal screening tests. Treatment and management of syphilis in HIV positive pregnant women is the same as per HIV negative women.

10.3.6 Management of sexual contacts and other children

- Partner notification or contact tracing must be undertaken by the team leading the care of the pregnant woman, usually a sexual health physician or infectious disease physician.

- Empirically treat all sexual contacts of the affected patient from within 3 months of a diagnosis of early syphilis and some cases of syphilis of unknown acquisition date regardless of negative serology.[21]

- Notification intervals are given below:

Table 2

Stage of affected person	Look-back period
Primary	Duration of symptoms plus 3 months
Secondary	Duration of symptoms plus 6 months
Early latent	12 months
Late syphilis	Test long term partners and treat if positive

Adapted from New Zealand Sexual Health Society Best Practice guidelines 2017[21]

- Any older children of the pregnant woman should be tested for syphilis if there is no negative syphilis serology on record since their date of birth.
- In some cases, all children (including non-biologic) living in a household of a case of infectious syphilis may need to be tested. It is outside the scope of these guidelines to address this here.
- Please discuss with a sexual health physician or a paediatric infectious diseases physician in these situations.

10.3.7 Management of pregnant sexual contacts of infectious syphilis

- There are no studies looking at the management of pregnant sexual contacts of a case of infectious syphilis. These should be managed on a case by case basis after discussion with a sexual health physician.
- A repeat syphilis test is indicated when such a person presents to a healthcare professional.

- If their test is reactive then the woman is managed as a case of syphilis in pregnancy.
- If their test is negative and their last sexual contact with the infectious case is more than 90 days, then infection is ruled out. However, careful consideration must be given to the possibility of re-exposure to syphilis in current pregnancy.
- If their test is negative, and if their last sexual contact with the infectious case was less than 90 days previously, then treatment is indicated as given below.
  Recommended treatment is **as per management of early syphilis:**
  - **Trimester 1 or 2 (up to and including 27 weeks)**: Benzathine benzylpenicillin tetrahydrate 2,400,000 units/4.6 ml intramuscularly as a **single dose**
  - **Trimester 3 (from week 28 to term):** Benzathine benzylpenicillin tetrahydrate 2,400,000 units/4.6 ml intramuscularly, on days 1 and 8 (**two doses**)

- Follow up of treated pregnant contacts, who may have been incubating syphilis before tests become reactive is not known. These women require retesting for syphilis after the incubation period (3 months) and possibly at the time of time of birth.
- We recommend that advice is sought from a clinician experienced in managing syphilis in pregnancy.
- If the woman's test is reactive at any time, then the neonate will also need to be tested.

10.3.8 Follow up

- A multidisciplinary team with good communication between all team members is essential for the management of a case of syphilis in pregnancy.
- Following treatment, repeat RPR titres should be done at 28-32 weeks gestation (as a minimum) and immediately following birth.
- Women at high risk of re-infection (see Appendix 3) will require monthly RPR monitoring and if the RPR starts to rise, it would be prudent to retreat the woman.
- Ensure that women who are treated for syphilis in the first trimester have been referred to the secondary obstetric service if not already under their care.
- It is also important to discuss and identify a care plan with the paediatric/ neonatology team antenatally rather than following the birth.
- It is important that one team (usually the maternal treating team – sexual health physician/infectious diseases physician) takes responsibility for coordinating the care of the woman and liaising with the obstetric, midwifery, paediatric and general practice teams to ensure that treatment, contact tracing and follow up of the treated woman takes place.
- Paediatric teams are best placed to coordinate care and follow up of the new born as appropriate.
- The care plan (see attached example, Appendix 1), should be shared with all clinicians involved in the woman's care. The plan should be available in the hospital notes and the woman's own clinical record and distributed to the multidisciplinary team.

- Maternal treatment usually adequately treats both the woman and her fetus; however, **fetal treatment failure** is possible in the following situations:
  a) Maternal treatment <30 days before birth
  b) Primary or secondary syphilis in the pregnant woman
  c) High RPR at treatment and at birth (> 1:4)
  d) Fetal involvement seen on ultrasound
  e) Treatment with a non-penicillin agent
  f) Pre-term birth <36 weeks

- Pregnancies showing fetal involvement by ultrasound may need more frequent ultrasound examinations to assess fetal well-being and the fetal response to treatment.

10.3.9 Labour and birth

- Advise women treated for syphilis in pregnancy that they can expect to have usual intrapartum care for labour and birth.
- Breastfeeding is not contraindicated unless there is an active syphilis lesion on the breast.
- Send the placenta for histology and syphilis PCR testing if congenital infection is suspected (symptomatic babies, some stillbirths and high-risk situations -Section 11). Liaise with your laboratory if these tests are not done locally.
- Prior to birth, the paediatric team should be notified about the woman's syphilis stage, treatment, and fetal ultrasound findings. If this has not been undertaken prior to birth then the paediatric team should be notified during labour or immediately following the birth.

10.3.10 Contact Precautions

- Standard contact precautions are recommended for all women during birth, including infants with suspected or confirmed congenital syphilis.[17] Contact precautions should be taken when caring for women or babies with congenital, primary, and secondary syphilis with skin and mucous membrane lesions until 24 hours of treatment has been completed. This is because moist open lesions, secretions, and possibly blood are infectious when syphilis is untreated.

- Health care professionals are advised to seek help from their occupational health teams if inadvertently exposed to syphilis (e.g. handling or examining an infectious neonate without wearing gloves prior to 24 hours after administration of first dose of penicillin).

10.3.11 Handling of placenta (whenua)

- Whenua has particular importance to Māori people. Many women and whānau may wish to retain her placenta for burial.

- The placenta may also be required for further testing if congenital infection is suspected. The placenta and also the amniotic fluid could also be infectious.
- In cases where the placenta is needed for further testing, this should be discussed with the woman and her consent obtained and wishes known regarding return or disposal of the placenta.
- Discussion with a sexual health physician / infectious diseases physician is recommended on a case by case basis to determine if a particular woman's placenta is likely to be infectious.
- Gloves should be worn by health care professionals and the woman or her whānau when handling the placenta. The woman and her whānau should be advised to store and transport whenua/placenta in a leakproof container.

11. Care of the new-born (birth to 1 month)

Women with positive syphilis serology who have not met the criteria for adequately treated syphilis (Section 10.3.1) should have clear documentation in their antenatal record and birth/ care plan that their baby will require assessment and possible treatment at birth. The new-born should be assessed and examined by a paediatrician or neonatologist with serological blood tests obtained from the infant, to assess for symptoms, signs and laboratory evidence of congenital syphilis.

- **Early discussion with a neonatologist / paediatric infectious diseases physician experienced in the diagnosis and management of congenital syphilis is recommended.**

- **Auckland DHB (ADHB) has a nationwide 24/7 paediatric infectious diseases team on call for advice via ADHB switchboard: 09 367 0000**.
- Many DHBs may have their own paediatric infectious disease service- refer to your local DHB pathway.

Cord blood is not appropriate to be used for testing due to possible contamination from maternal blood and Wharton's Jelly. Serum from the neonate is required for serology. Take blood from the mother at the time of birth to be processed by the same lab to avoid inter-lab variability of non-treponemal tests.

Indications for treatment of babies at birth are often evident antenatally unless syphilis diagnosis was at or following the birth.

Risks for congenital syphilis:

Low risk:

- mother is treated appropriately >4 weeks before birth
- treatment completed > 4 weeks before birth
- mother treated with the correct penicillin regimen for the stage of syphilis

- maternal 4-fold drop in RPR achieved
- final RPR titre ≤ 1:4 (VDRL 1:2)

High risk: situations where infants require further evaluation and treatment at birth include the following:

- Maternal syphilis not treated or inadequately treated, or treatment inadequately documented
- Maternal syphilis treated but with inadequate follow-up or without a satisfactory 4-fold drop in RPR titre
- Treatment of syphilis in pregnancy with a non-penicillin regimen including ceftriaxone
- Treatment of the mother < 30 days prior to the birth (maternal treatment unlikely to have adequately treated the fetus)
- Final RPR titre > 1:4 (VDRL > 1:2)
- Abnormal fetal ultrasound findings

Infants born to mothers with syphilis and HIV require the same evaluation, therapy or follow-up as is recommended for all infants exposed to syphilis in-utero.[17] These infants will require additional tests and treatment for exposure to HIV in-utero, which is outside the scope of these guidelines.

Physical signs of early congenital syphilis

The majority of neonates with congenital syphilis will have no signs or symptoms at the time of birth.[11,14] Many signs are also non-specific and may mimic other conditions.

All neonates born to women who have had syphilis during pregnancy should be assessed at birth by a neonatologist or paediatrician.

Early signs:

- Hepatosplenomegaly, Hepatitis, Jaundice
- Inflammation of long bones (osteochondritis, perichondritis); failure to move an extremity (pseudoparalysis of Parrot)
- Skin rash or mouth lesions – usually maculopapular; palms and soles of feet may be red, swollen or mottled; vesicles or bullae may be present with peeling; condylomata lata (flat wart like in moist areas such as perineum)
- Low birth weight, failure to thrive (slow weight gain)
- Pneumonitis
- Rhinitis, ulceration of nasal mucosa - "snuffles" (usually after the first week of life),
- Generalised lymphadenopathy
- Haematologic disturbances (anaemia, haemolysis, disseminated intravascular coagulation, thrombocytopenia)
- Non-immune, hydrops
- Nephrotic syndrome
- Necrotising funisitis – inflammation of the umbilical cord
- Fever

Investigations:

- **Initial blood tests**
    - Paired venous blood samples: RPR serology paired with mother
        - Send a neonatal venous blood sample for syphilis serology: request serum treponemal EIA, RPR, treponemal IgM (available through select laboratories in NZ). Take blood from the neonate, not the umbilical cord.
        - Send a maternal venous blood sample for serum RPR at the time of birth if no result available within the past 4 weeks from the same lab

- **Additional tests on infant if muco-cutaneous lesions present**
    - Direct *T. Pallidum* PCR‡ assay from lesions and / or nasal discharge (if present), placental tissue and / or amniotic fluid,
        - Use flocked viral swab (as if taking Herpes Simplex Virus PCR) (available through select laboratories in NZ)

‡ PCR testing of placenta/ amniotic fluid (if available) and mucocutaneous lesions is indicated in high-risk situations for congenital syphilis and/or symptomatic babies.

- **Further tests if treatment indicated (see below & algorithm)**
    - Infant CSF examination: request cell count, protein, VDRL
    - Full blood count, urea, electrolytes, creatinine, liver function tests
    - Long bone X-rays for osteochondritis & periostitis

- **Other tests which may be required:**
    - Chest X-Ray (cardiomegaly)
    - Neuroimaging
    - Ophthalmologic (interstitial keratitis)
    - Formal audiology examination (sensorineural (8^{th}) nerve deafness)

- **Infection control of neonate**
  Gloves should be worn for handling babies with suspected congenital syphilis as moist open lesions of skin and mucous membranes, secretions and possibly blood are contagious until 24hrs of penicillin treatment has been completed.

11.1 Infant assessment and management summary (infants <30days old)

Table 3

Category	Findings	Evaluation	Treatment	Follow up††
Proven, or highly probable congenital syphilis	• Abnormal physical examination consistent with congenital syphilis OR • A serum RPR titre fourfold high than the mother's titre on 2 occasions (e.g. mother's RPR 1:4, infants 1:16) or infant IgM positive OR • *T. pallidum* PCR assay of lesions or body fluids reactive	• CSF analysis (CSF VDRL, cell count, and protein) • FBC, EUC, LFT • Long-bone X-Rays • Other tests if needed: -Chest X Ray -Neuroimaging • Ophthalmologic examination • Formal audiologic examination • Placental histology and syphilis PCR	Benzylpenicillin 50,000units (30mg)/kg/dose IV every 12 hours during the first 7 days of life AND every 8 hours thereafter for a total of 10 days *****	1) Paediatric review at 6wks, 3mths, 5-6 mths and 12-18 mths of life. 2) (RPR expected to be negative at 6 months) 3) IF congenital neurosyphilis diagnosed at birth- repeat CSF analysis every 6 months until normal parameters 4) If infant RPR increasing or not decreasing may need repeat LP / retreatment
Asymptomatic possible congenital syphilis	• Normal clinical examination AND • serum RPR equal to or less than fourfold the maternal titre AND ONE OF THE FOLLOWING	• CSF analysis (CSF VDRL, cell count, and protein) • FBC, EUC, LFT • Long-bone X-Rays • Placental histology and syphilis PCR	Benzylpenicillin 50,000units(30mg)/kg/dose IV every 12 hours during the first 7 days of life AND every 8 hours thereafter for a total of 10 days***** Note: For some infants where CSF examination and other investigations normal and where follow up can be assured, then	1) Paediatric review at 6wks, 3mths, 5-6 and 12-18 mths of life with repeat RPR (RPR expected to be negative at 6 months) 2) IF congenital neurosyphilis diagnosed at birth- repeat CSF analysis every 6months until normal

	• Mother not treated, inadequately treated or no documentation of treatment OR • Mother treated with a non-penicillin regimen OR • Mother received recommended treatment <4 weeks before delivery		benzathine benzylpenicillin tetrahydrate 50,000U/kg IM as a single dose may be used after discussion with Paediatric ID specialist **#**	
Congenital syphilis less likely	• Normal infant examination AND • Serum RPR titre equal to or less than fourfold the maternal titre AND • Mother treated appropriately during pregnancy for stage of infection and treatment was administered > 4 weeks before delivery	None needed	Repeat serology at 3 months OR if any concern regarding follow up or lack of required maternal testing then **GIVE** benzathine benzylpenicillin tetrahydrate 50,000units/kg IM as a single dose **#**	1) Repeat syphilis serology at 3 months – if all negative – discharge 2) If syphilis serology reactive then repeat at 3 monthly intervals until negative 3) RPR is expected to be non-reactive at 6 months - any passive cross over of treponemal antibodies will be negative by 15 months of life.

	AND • Mother has no evidence of reinfection or relapse			

NB Ensure correct form of parenteral penicillin is prescribed and administered. Benzathine benzylpenicillin tetrahydrate is a long-acting injection intended for intramuscular use. Benzylpenicillin is intended for intravenous use.

(Adapted and modified from AAP Red Book[17] ASID[28] and CDC 2015[20])

Table 3 Footnotes

** Aqueous procaine penicillin G 50,000 units (50mg)/kg IM in a single daily dose for ten days is an alternative treatment to intravenous benzyl penicillin in the asymptomatic infant with probable or possible congenital syphilis*

 # Benzathine benzylpenicillin tetrahydrate SINGLE LONG ACTING Intramuscular dose = 50,000 units/kg
To be prescribed in units only; for mg conversions REFER to NZ FORMULARY FOR CHILDREN
Decant contents of 1,200,000 units/2.3mL syringe into a graduated syringe
Calibrate syringe to correct volume using a concentration of 500,000 units/mL to calculate the volume to administer(NB the concentration of the injection has been rounded to 500,000 units/mL for ease of calculation and administration)
Inject dose slowly, at a steady rate, preferably over at least 2 – 3 minutes, deep into the midlateral aspect of the thigh for infants
To reduce pain of deep IM injections allow syringe to reach room temperate before administration (can give stat dose of oral sucrose as per local protocol just prior to injection)

†† It is the responsibility of the respective Paediatric Teams to ensure adequate follow up for infants until discharge as interpretation of infant serology is complex. However, depending on local service provision some follow up visits for asymptomatic infants may be arranged through Primary Care along with Well Child Tamariki Ora visits with Paediatric oversight of test results.

11.2 Infant Management Summary

- If more than 1 day of therapy is missed, the entire course should be restarted.
- Infant treponemal tests can be positive due to passively transferred antibodies but this should usually disappear by 15 months of age.
- Positive treponemal tests after 18 months is diagnostic of congenital syphilis and is likely to persist despite adequate treatment.
- Non treponemal tests (RPR or VDRL) are used for monitoring treatment response.
- Serum RPR should be nonreactive / negative by 6 months. Infants with increasing RPR titres or persistent stable RPR titres 6-12 months after retreatment should be revaluated including CSF examination and retreatment need to be considered after discussion with Paediatric ID teams.
- Babies with possible, proven or highly probable congenital syphilis should be followed up by the Paediatrics team and have repeat serology at 6weeks, 3months and 6 months of age or until RPR non-reactive.
- For neurosyphilis, repeat CSF at 6 months.

12. Notification and surveillance

All cases of infectious syphilis and congenital syphilis (confirmed and probable cases as per ESR case definition) are required to be notified under the Health Act 1956 (Section C).
The treating teams take responsibility for this.

- Infectious diseases or sexual health teams should notify maternal cases.
- Paediatric or neonatology teams should notify congenital cases.
- Paediatricians and neonatologists should also fill in New Zealand Paediatric Surveillance Unit (NZPSU) forms, available at https://www.otago.ac.nz/nzpsu/current-studies/index.html.
- Midwives who receive positive syphilis screening results refer to specialists who will be responsible for notification.
- The forms can be accessed on the ESR STI surveillance page: https://surv.esr.cri.nz/public_health_surveillance/sti_surveillance.php.
- Case definitions for infectious syphilis and congenital syphilis for ESR are available on: https://www.health.govt.nz/our-work/diseases-and-conditions/communicable-disease-control-manual/syphilis-case-definition-only.

Notification is mandatory.

References

1. The Institute of Environmental Science and Research Limited (ESR). Surveillance of Sexually Transmitted Infections. Available on-line on: https://surv.esr.cri.nz/public_health_surveillance/sti_surveillance.php. Accessed on 26/8/2020.
2. Larkin H, Shields J,Anda RF. The Health and Social Consequences of Adverse Childhood Experiences (ACE) Across the Lifespan: An Introduction to Prevention and Intervention in the Community. J Prev Interv Community. 2012:40;263-70.
3. Institute of Medicine (US) Committee on Prevention and Control of Sexually Transmitted Diseases; Eng TR, Butler WT, editors. The Hidden Epidemic: Confronting Sexually Transmitted Diseases. Washington (DC): National Academies Press (US); 1997. 3, Factors that Contribute to the Hidden Epidemic. Available from: https://www.ncbi.nlm.nih.gov/books/NBK232936/. Accessed on 26/8/2020.
4. Cunningham SD, Olthoff G, Burnett P, Rompalo AM, Ellen JM. Evidence of heterosexual bridging among syphilis-positive men who have sex with men. Sex Transm Infect. 2006; 82:444–5.
5. 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(3):217–26.
6. Qin J, Yang T, Xiao S, Tan H, Feng T, et al. Reported Estimates of Adverse Pregnancy Outcomes among Women with and without Syphilis: A Systematic Review and Meta-Analysis. PLoS ONE 2014;9(7): e102203.
7. Berman S. M. Maternal syphilis: pathophysiology and treatment. Bull World Health Organ.2004; 82(6): 433–8.
8. Holmes KT, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, et al., editors. Sexually transmitted diseases. 4th ed. New York: McGraw-Hill; 2008. Chapter 82
9. Sheffield JS, Sánchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. Am J Obstet Gynecol. 2002; 186:569-73.
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.
11. Kollmann TR, Dobson S. Syphilis. In: Infectious Diseases of the Fetus and Newborn Infant, 7th, Remington JS, Klein JO, Wilson CB, et al (Eds), Elsevier Saunders, Philadelphia 2011. p.524.
12. Rac MWF, Bryant SN, McIntire DD, et al. Progression of ultrasound findings of fetal syphilis after maternal treatment. Am J Obstet Gynecol. 2014;211:426.e1-6.
13. Johnson C.T., Sheffield J.S. In: Obstetric Imaging: Fetal Diagnosis and Care: Congenital Syphilis: Second Edition, 2018.
14. Dobson SR, Sanchez PJ. Syphilis. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 8th ed, Cherry JD, Harrison GJ, Kaplan SL, et al (Eds), Elsevier Saunders, Philadelphia 2019. p.1268.
15. Herremans, T., Kortbeek, L. & Notermans, D.W. A review of diagnostic tests for congenital syphilis in newborns. Eur J Clin Microbiol Infect Dis. 2010;29:495-501.
16. Azariah, S. An audit of patients treated for syphilis at Auckland Sexual Health Service. NZMJ. 2010;123(1315):55-64.
17. American Academy of Pediatrics. Syphilis. In: Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Itasca, IL 2018. p.773
18. Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA. 2014;312(18):1905–17.
19. Walker GJA. Antibiotics for syphilis diagnosed during pregnancy. Cochrane Database Syst Rev. 2001; (3):CD001143.

20. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines 2015: Syphilis. Available on-line on https://www.cdc.gov/std/tg2015/tg-2015-print.pdf. Accessed on 26/8/2020.
21. New Zealand Sexual Health Society Best Practice guidelines 2017. Available on-lineat: www.nzshs.org/docman/guidelines/management-of-sexual-health-conditions/syphilis/174-syphilis-guideline/file. Accessed on 26/8/2020.
22. Kingston M, French P, Higgins S, et al. UK national guidelines on the management of syphilis 2015. Int J STD AIDS. 2016;27:421-6.
23. Nathan L, Bawdon RE, Sidawi JE, Stettler RW, McIntire DM, Wendel Jr GD. Penicillin levels following the administration of benzathine penicillin G in pregnancy. Obstet Gynecol 1993;82:338-42.
24. G Donders, J Desmyter, P Hooft, H Dewet. Apparent Failure of One Injection of Benzathine Penicillin G for Syphilis During Pregnancy in Human Immunodeficiency Virus-Seronegative African Women. Sex Transm Dis.: 1997;24(2):94–101.
25. Ministry of Health. 2019. National Syphilis Action Plan: An action plan to stop the syphilis epidemic in New Zealand. Wellington: Ministry of Health.
26. Congenital syphilis guidelines for the Northern territory, accessed at: https://digitallibrary.health.nt.gov.au/prodjspui/handle/10137/707
27. Roberts CP, Raich A, Stafylis C, Klausner JD. Alternative Treatments for Syphilis During Pregnancy; Sex Transm Dis. 2019;46(10):637-40.
28. Australasian Society of Infectious diseases Management of Perinatal Infections 2014 Available on-line at https://www.asid.net.au/documents/item/368. Accessed on 26/8/2020.
29. From Congenital Toxoplasmosis, Syphilis, Malaria, and Tuberculosis: Chapter 38 Marian G. Michaels, Pablo Sanchez and P. Ling Lin. Avery's Diseases of the Newborn, 38, 527-552.e6
30. Syphilis: testing for "the great imitator"- BPAC. Available on-line at: https://bpac.org.nz/BT/2012/June/06_syphilis.aspx. Accessed 26/8/2020.
31. Ghanem KG. Management of Adult Syphilis: Key Questions to Inform the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis. 2015;61(suppl_8), S818–S36.
32. Lin JS, Eder ML, Bean SI. Screening for Syphilis Infection in Pregnant Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018;320(9):918–25.
33. Department of Health (2019) Clinical Practice Guidelines: Pregnancy Care. Canberra: Australian Government Department of Health. Available on-line at: https://www.health.gov.au/resources/pregnancy-care-guidelines/part-f-routine-maternal-health-tests/syphilis. Accessed on 26/8/2020.

Appendix 1 – Syphilis Care Plan

CARE PLAN FOR WOMEN WITH SYPHILIS DURING PREGNANCY

Mother's Details	
Name	
Address	
DOB	
NHI	
Phone number(s)	
Estimated Due Date	

Labour and birth Team Actions	
☐	No need to contact on-call paediatric team from syphilis viewpoint *(woman treated prior to current pregnancy and no risk of re-infection)*
☐	Contact on-call paediatric team when baby is born
☐	Send placenta for histology and treponemal PCR if syphilis treatment indicated for infant

Congenital Syphilis Risk – Pre-birth assessment

Congenital syphilis unlikely		**Higher risk of congenital syphilis**	
☐	Maternal treatment completed	☐	**Maternal infection: partial or no treatment***
☐	Treated with penicillin	☐	**Treated with non-penicillin***
☐	Treatment completed >30 days pre-delivery	☐	**Treatment <30 days before delivery***
☐	4x drop in RPR achieved	☐	4x drop in RPR not achieved
☐	Final RPR titre ≤1:4 (VDRL 1:2)	☐	Final RPR titre >1 in 4 (VDRL >1 in 2)
		☐	Abnormal fetal ultrasound findings

***The presence of any of the 'bold asterisk' factors above means inadequate maternal treatment & requires neonatal treatment at birth. Also, congenital syphilis can still occur despite the absence of the three 'bold' factors.

Maternal Syphilis Care

[Include stage, treatment & treatment dates, most recent RPR, whether coded or under & any concerns e.g. re-infection risk from partner, treatment late in pregnancy, etc]

STAGE					
Date	**RPR**	**Treatment given**	**Batch No. & expiry**	**Contact tracing**	**Comments/concerns**

Advice to Paediatricians

☐	Low risk: assess infant clinically; if no physical signs of syphilis check '**initial blood tests', OR**
☐	High risk: treat infant at birth after clinical assessment, '**initial blood tests' and 'further tests'**
Please discuss all infant blood test results with Paediatric Team.	
Sexual Health Physician:	
Signed:	
Date:	

Birth Plan Form to be given to the woman with copies to:

- Paediatric SMO
- LMC
- LMC midwife
- Obstetric SMO
- GP

A. Physical Signs of Early Congenital Syphilis

- Jaundice, anaemia, generalised lymphadenopathy, hepatosplenomegaly, non-immune hydrops, pyrexia, failure to move an extremity (pseudoparalysis of Parrot), low birth weight.
- Skin rash: usually maculo-papular but almost any type of rash is possible; palms and soles may be red, mottled and swollen. Vesicles or bullae may be present.

- Condylomata lata (flat, wart-like plaques in moist areas such as perineum).
- Osteochondritis, periosteitis (elbows, knees, wrists).
- Ulceration of nasal mucosa, rhinitis ('snuffles' usually after the first week of life).

More than half of neonates with congenital syphilis are normal on initial examination.

B. Initial Blood Tests

1) Paired venous blood samples:

- Send a neonatal venous blood sample for syphilis serology; request serum treponemal EIA + RPR + treponemal IgM (available from select NZ Laboratories). Take blood from the neonate, not the umbilical cord.
- Send a maternal venous blood sample for serum RPR if no result within last 4 weeks available from the same lab.

2) Additional Tests on Infant if Lesions Present*

Take *T pallidum* polymerase chain reaction (PCR) test from lesions &/or nasal discharge – use viral swab (i.e. as if taking HSV PCR); (available via select NZ laboratories)
** lesions of congenital syphilis are infectious; manage infant with contact precautions*

C. Further Tests if Treatment Indicated (see below)

- FBC, UCE, LFT, ALT/AST
- Lumbar puncture for CSF: request cell count, protein, CSF VDRL
- Long bone x-rays for osteochondritis & periostitis
- Chest x-ray for cardiomegaly
- Ophthalmology assessment for interstitial keratitis
- Audiology

D. Indications for Further Tests and Newborn Treatment

- Mother inadequately treated (Sexual Health/ID consultant will advise).
- Infant has clinical signs consistent with syphilis (Paediatric team will advise).
- Infant's RPR/VDRL titre 4x mother's (e.g. mother's RPR 1:4, infant's RPR 1:16). (Sample from mother to be taken no greater than 4 weeks before that of infant)
- Infant has positive treponemal IgM test together with corroborative history, clinical signs.
- Infant has positive T pallidum PCR test together with corroborative history, clinical signs.
- Placental T pallidum PCR positive or histological evidence of congenital infection will also lead to treatment of asymptomatic infants with other normal investigations.

E. Treatment of Neonates and Children

Recommended doses of benzylpenicillin (penicillin G)

- Neonate under 7 days 30 mg/kg/dose every 12 hours for 7 days AND every 8 hours thereafter for a total of 10 days
- Neonate 7–28 days 30 mg/kg/dose every 8 hours for 10 days

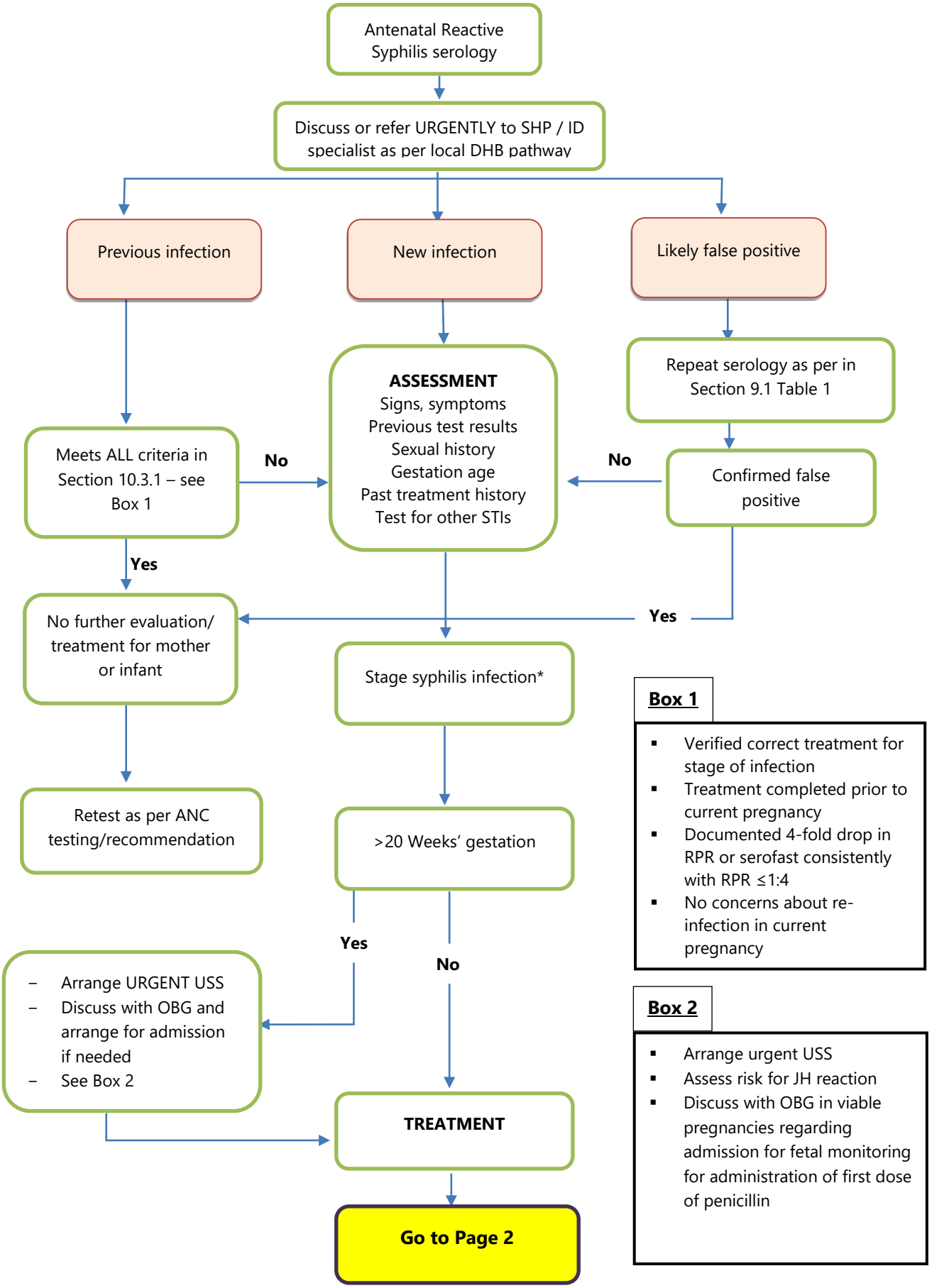
F. Infant follow up

1. Proven, highly probable, congenital syphilis		2. Asymptomatic, possible, congenital syphilis		3. Congenital syphilis less likely	
6 weeks		6 weeks		Month 3	
☐	Check RPR	☐	Check RPR	☐	Repeat RPR and IgM to exclude late seroconversion
☐		☐		☐	Discharge if results negative
Month 3		Month 3		**OR**	
☐	Check RPR	☐	Check RPR	☐	RPR and/or IgM positive; discuss with Paediatric Team
Month 6		Month 6			
☐		☐	Check RPR, if negative discharge, if positive repeat at 12 months		
Month 12		Month 12			
☐	Check RPR. Discharge if RPR has achieved sustained 4x drop from peak level	☐	RPR negative, no further follow up OR		
		☐	RPR still positive, discuss with Paediatric Team		
			*Note: the RPR is usually negative by six months		

Neonatal RPR should be negative by 6 months of age and the TPPA should be negative by 18 months of age; early reactive results may as a result of passive transfer of maternal antibodies.

Appendix 2 - Antenatal Syphilis Management Flowchart

Appendix 2 – Antenatal Syphilis Management Flowchart



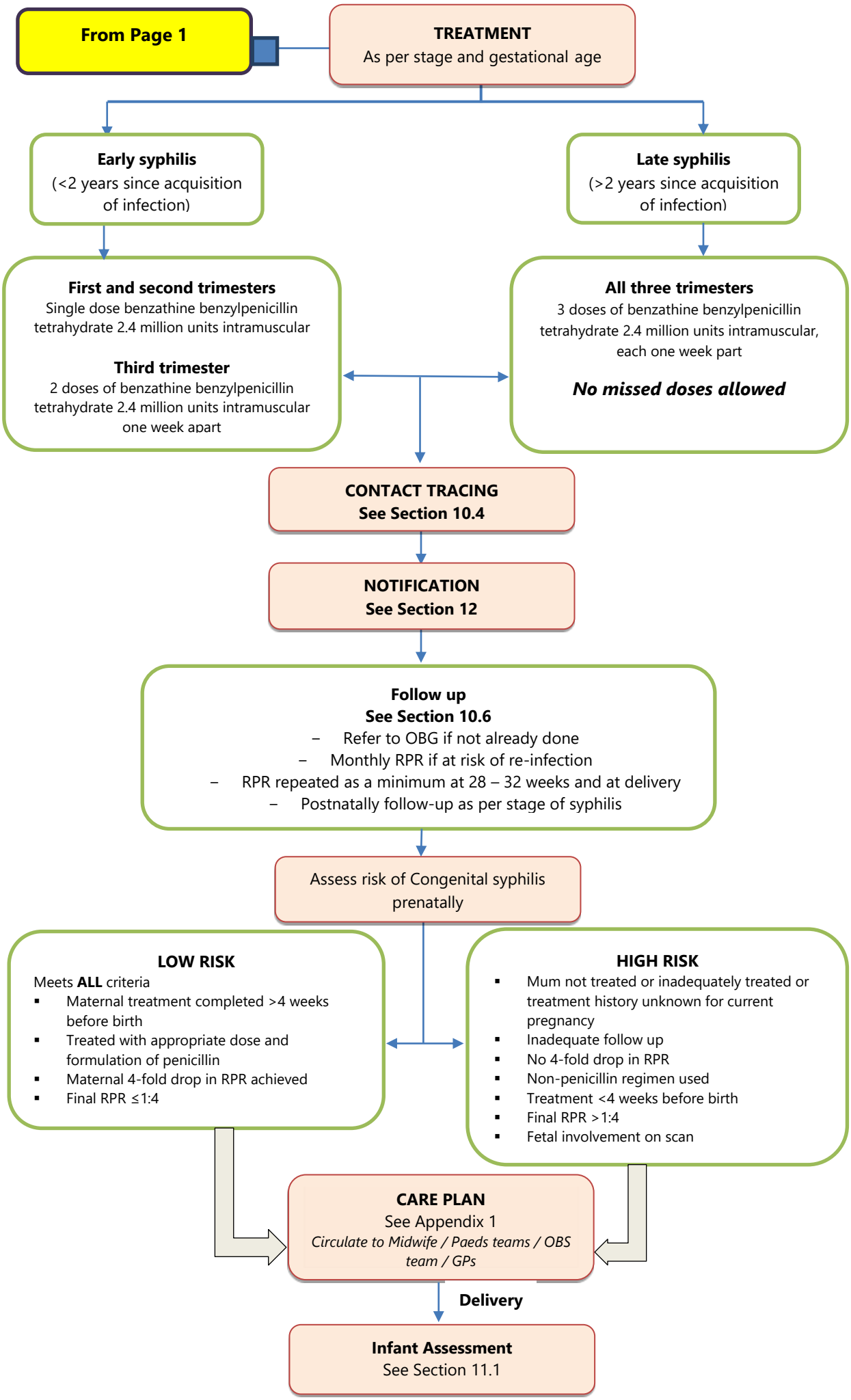
Box 1

- Verified correct treatment for stage of infection
- Treatment completed prior to current pregnancy
- Documented 4-fold drop in RPR or serofast consistently with RPR ≤1:4
- No concerns about re-infection in current pregnancy

Box 2

- Arrange urgent USS
- Assess risk for JH reaction
- Discuss with OBG in viable pregnancies regarding admission for fetal monitoring for administration of first dose of penicillin

*Women with neurological signs/symptoms will need further assessment to rule out neurosyphilis – see Section 10.2.3


From Page 1
TREATMENT
As per stage and gestational age
Early syphilis
(<2 years since acquisition of infection)
Late syphilis
(>2 years since acquisition of infection)
First and second trimesters
Single dose benzathine benzylpenicillin tetrahydrate 2.4 million units intramuscular
Third trimester
2 doses of benzathine benzylpenicillin tetrahydrate 2.4 million units intramuscular one week apart
All three trimesters
3 doses of benzathine benzylpenicillin tetrahydrate 2.4 million units intramuscular, each one week part
No missed doses allowed
CONTACT TRACING
See Section 10.4
NOTIFICATION
See Section 12
Follow up
See Section 10.6
– Refer to OBG if not already done
– Monthly RPR if at risk of re-infection
– RPR repeated as a minimum at 28 – 32 weeks and at delivery
– Postnatally follow-up as per stage of syphilis
Assess risk of Congenital syphilis prenatally
LOW RISK
Meets ALL criteria
Maternal treatment completed >4 weeks before birth
Treated with appropriate dose and formulation of penicillin
Maternal 4-fold drop in RPR achieved
Final RPR ≤1:4
HIGH RISK
Mum not treated or inadequately treated or treatment history unknown for current pregnancy
Inadequate follow up
No 4-fold drop in RPR
Non-penicillin regimen used
Treatment <4 weeks before birth
Final RPR >1:4
Fetal involvement on scan
CARE PLAN
See Appendix 1
Circulate to Midwife / Paeds teams / OBS team / GPs
Delivery
Infant Assessment
See Section 11.1

Appendix 3 – Screening and testing for syphilis in pregnancy

1) **All pregnant women in New Zealand are routinely offered a syphilis test as part of their first antenatal bloods.**
   This also includes pregnant women who are considering termination of their pregnancy. The evidence for and the cost-effectiveness of universal syphilis testing at first antenatal contact is well established.[32]
   Additional syphilis testing is also needed for pregnant women with signs of primary or secondary syphilis (see Section 8.2) and for women with sexual partners who have infectious syphilis.

2) Offer a syphilis test to any woman who has had a **stillbirth at 20 weeks gestation or later**, at the time of birth.

3) Offer a syphilis test to any pregnant woman admitted to a maternity hospital without a documented syphilis test/ result prior to discharge.

4) A syphilis test can be done at any time at the request of the pregnant woman.

Retesting pregnant women at risk of syphilis infection or re-infection

Re-testing is also recommended by many guidelines[20-22] for 'high risk women' or women living in 'high prevalence' areas in the third trimester (28-32 weeks gestation) and at birth.[20,33]

New Zealand has no official definition for 'high risk' women or 'high prevalence' areas based on its own epidemiological data. Nearly all congenital cases of syphilis have been in Māori and Pacific Islander whānau.

29% (4/14 cases since 2016) of congenital syphilis infections in New Zealand occurred in women who had a negative syphilis serology in first trimester (personal communication, Dr Jill Sherwood, ESR). Clinicians who managed many of these women could not identify risk factors for syphilis infection or re-infection that the women themselves were aware of.

Many jurisdictions in the United States and Australia and other countries routinely offer all pregnant women a second syphilis test in early third trimester and some also at the time of birth.

Many clinicians who worked on these guidelines support a routine offer of a second syphilis test in early third trimester. However, there was no consensus for this practice among clinicians or laboratories. The cost effectiveness of this strategy in New Zealand cultural setting has not been assessed.

Ministry of Health maternity group and the National Screening Unit (NSU) is expected to provide some guidance for this in future.

Based on overseas studies and guidelines, women with the following characteristics may be considered at higher risk of syphilis infection and re-infection. In the interim period, while awaiting New Zealand specific retesting guidelines, offer these women **further syphilis testing at 28-32 weeks and at birth.**

- No or inconsistent antenatal care
- A sexually transmitted infection (STI) diagnosed during the past year
- Current recreational drug use
- Incarceration in the past year
- Currently experiencing homelessness or no fixed abode
- Multiple sexual partners
- A sexual partner who has any of the following risk factors: STI in past year, multiple sexual partners, current recreational drug use, recent incarceration, homelessness or is a man who also has sex with men.

Please be aware that a woman may not be aware of all her risk factors for syphilis infection or re-infection. Therefore, it would be prudent for clinicians to exercise a low threshold for offering pregnant women repeat syphilis testing.