Syphilis

Manitoba
Public Health Branch

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1. Summary of Updates

December 2024

- Minor updates to section 7.2, reflecting changes to CPL process for syphilis testing.

January 2023

Minor updates:

- Section 3.4 – Note added as clarification to the case definition for early latent syphilis - included four-fold or greater increase in titre over the last known non-treponemal test.
- Sections 4.2, 8.5 – Update to new provider reporting form: MHSU 6781- The Provider Report Form for Sexually Transmitted and Blood-Borne Infections (STBBI) and STI Treatment.
- Sections 8.3.7, 8.3.10 - Minor editorial clarifications on treatment during pregnancy. Removal of recommendation to stay near tertiary center post-treatment in pregnancy based on local data for Jarisch-Herxheimer reaction and harm of delaying treatment.
- Section 10 - Updates to documentation guidelines, including new process for provider forms and follow-up recommendations.

July 2022

The protocol review process resulted in numerous updates throughout the document, including:

- Revised guidance in the previous letters to healthcare providers has been incorporated into the relevant sections of the protocol.
- Section 3.1: Clarification of staging of congenital syphilis in the case of non-reactive serology at 18-24 months of age.
- Section 6.4: Advice on staging (further clarification on early latent and late latent) and treatment of asymptomatic individuals (also included in Sections 3.4).
- Section 8.3.5: How to administer penicillin G benzathine.
- Section 9: Key Investigations for Public Health Response, including new documentation guidance for public health.

Summary of Addenda added to Previous Version of the Protocol (July 2014)

- Updates to Syphilis Protocol Congenital Syphilis and Syphilitic Stillbirth Case Definitions and Reporting (October 12, 2021)
- Clarification of the treatment of syphilis in pregnancy greater than 20 weeks gestation (October 20, 2020)
- Syphilis Infection in Pregnancy and Congenital Syphilis in Manitoba (July 21, 2020)

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- Letter to Healthcare Providers Re: Clarification of the Treatment of Primary, Secondary or Early Latent Syphilis in Pregnancy
  (July 15, 2019)
- Letter to Healthcare Providers Re: Congenital HIV and Congenital Syphilis in Manitoba
  (June 3, 2019)
- Letter to Healthcare Providers Re: Congenital Syphilis in Manitoba
  (February 25, 2019)
- Letter to Healthcare Providers Re: Syphilis Reporting and Case and Contact Investigation
  (March 1, 2016)
- Letter to Healthcare Providers Re: Provincial Response to Syphilis Outbreak – Management Tool Available
  (January 7, 2016)
- Update on Infectious Syphilis in Manitoba
  (December 2015)

2. Etiology

Syphilis is primarily a bacterial sexually transmitted infection (STI). Syphilis can also be acquired through congenital transmission to the newborn, and rarely through blood-borne transmission. It is a systemic disease caused by the spirochete *Treponema pallidum* subspecies *pallidum* (1). Syphilis occurs exclusively in humans; there is no animal reservoir (2).

Non-venereal treponemal infections cause pinta, yaws, and bejel. These diseases are endemic to some regions of the world and may be seen in Manitoba primarily as a result of immigration. Serologic testing cannot distinguish syphilis from these endemic treponematoses (3).

3. Case Definitions

3.1 Congenital Syphilis

3.1.1 Early Congenital Syphilis (within two years of birth*)*

Lab Confirmed Case - Early Congenital Syphilis (within two years of birth)

Identification of *T. pallidum* by dark-field microscopy[a], direct fluorescence antibody[b], or detection of *T. pallidum* deoxyribonucleic acid (DNA) by nucleic acid amplification test (NAAT) such as polymerase chain reaction (PCR) in an appropriate clinical specimen, or equivalent examination of material from nasal discharges, skin lesions, placenta or umbilical cord, or autopsy material of a neonate (up to four weeks of age).

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Note: A nasopharyngeal (NP) swab should also be collected for syphilis PCR as many cases are positive by this relatively non-invasive but less sensitive method. The specimen collection procedure is the same as the Cadham Provincial Laboratory (CPL) NP swab collection for respiratory virus detection described here:
https://www.gov.mb.ca/health/publichealth/cpl/docs/nasopharyngeal_collection.pdf

OR

Reactive serology (treponemal and nontreponemal) from venous blood (not cord blood) in an infant/child with or without clinical, other laboratory, or radiographic evidence consistent with congenital syphilis[c] but who has one or both of the following:

1) Rising syphilis serologic titres (at least four-fold higher) upon follow-up where there is evidence that the mother or birthing parent had a syphilis infection during pregnancy.

2) Titres greater than or equal to fourfold higher than those of the mother or birthing parent when collected at the same time or within a week, in the immediate post-natal period.

OR

Reactive serology (treponemal and nontreponemal) from venous blood (not cord blood) in an infant/child with clinical, other laboratory, or radiographic evidence consistent with congenital syphilis[c] whose mother or birthing parent was seropositive or PCR positive for syphilis during pregnancy, at delivery, or in the immediate post-partum period.

OR

A child who does not meet the above criteria but has persistently reactive treponemal serology between 18 and 24 months of age (regardless of treatment status and infectious status of the mother or birthing parent).

Probable Case - Early Congenital Syphilis (within two years of birth)[d]

Reactive serology (treponemal and nontreponemal) from venous blood (not cord blood) in an infant/child **without** clinical, laboratory, or radiographic manifestations of congenital syphilis whose mother or birthing parent had

- untreated or inadequately treated syphilis[e] prior to delivery

OR

- evidence of reinfection or relapse in the pregnancy following appropriate treatment (e.g., rising nontreponemal titres at least four-fold higher)

Note: A child that meets a probable case definition should remain staged as a probable case if testing at 18-24 months is negative. If they still have a reactive treponemal test at ≥ 18 months old, then their classification should be changed to “lab confirmed”.

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Lab Confirmed Case - Syphilitic Stillbirth

A fetal death that occurs after 20 weeks gestation with laboratory confirmation of infection (i.e., detection of *T. pallidum* DNA in an appropriate clinical specimen, direct fluorescent antibody[b] or equivalent examination of material from placenta, umbilical cord or autopsy material).

Note: In order to improve capture of congenital syphilis stillbirths, it is **critical that stillbirth investigation protocols include a swab (e.g., nasopharyngeal, placenta, oral, umbilical cord) for syphilis PCR testing.** Ensure that local stillbirth protocols include syphilis PCR testing of all stillbirths.

Probable Case - Syphilitic Stillbirth

A fetal death that occurs after 20 weeks gestation where the mother or birthing parent had untreated or inadequately treated syphilis prior to delivery OR whose mother or birthing parent had evidence of reinfection or relapse in pregnancy following appropriate treatment (such as rising nontreponemal titres at least four-fold higher), with no other cause of stillbirth established.

3.1.2 Late Congenital Syphilis (greater than two years after birth)

Lab Confirmed Case - Late Congenital Syphilis (greater than two years after birth)

Reactive treponemal serology (regardless of nontreponemal test reactivity) along with characteristic late manifestations of congenital syphilis[f] in a child whose mother or birthing parent was known or considered to be seropositive for syphilis during pregnancy, without documented evidence of adequate treatment,

AND

No other known source of exposure (i.e., infection must have occurred in utero).

3.2 Primary Syphilis

Lab Confirmed Case – Primary Syphilis

Identification of *T. pallidum* by dark-field microscopy[a], fluorescent antibody[b], or detection of *T. pallidum* DNA by NAAT (e.g., PCR), or equivalent examination of material from a chancre, consistent mucocutaneous lesion, or regional lymph node;

OR

Presence of one or more typical lesions (e.g., chancres), and reactive treponemal serology, regardless of nontreponemal test reactivity, in individuals with no previous history of syphilis;

OR

Presence of one or more typical lesions (e.g., chancres) and at least a fourfold (e.g., 1:8 to 1:32) increase in titre over the last known nontreponemal test, in individuals with a past history of (adequate) syphilis

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treatment (4).

3.3 Secondary Syphilis

Lab Confirmed Case – Secondary Syphilis

Identification of *T. pallidum* by dark-field microscopy[a], fluorescent antibody[b], or detection of *T. pallidum* DNA by NAAT, or equivalent examination of mucocutaneous lesions and condyloma lata and reactive serology (nontreponemal and treponemal);

OR

Presence of typical signs or symptoms of secondary syphilis (e.g., rash, mucocutaneous lesions, alopecia, loss of eyelashes and lateral third of eyebrows, iritis, generalized lymphadenopathy, fever, malaise, or splenomegaly); AND either a reactive serology (nontreponemal and treponemal) OR at least a fourfold (e.g., 1:8 to 1:32) increase in titre over the last known nontreponemal test (4).

3.4 Early Latent Syphilis (less than one year after infection)

Note: May include or be referred to as incubating syphilis. For provincial surveillance purposes, any cases reported as “incubating” will be categorized as early latent syphilis.

Lab Confirmed Case – Early Latent Syphilis

An asymptomatic person with reactive serology (treponemal and/or nontreponemal)[1] who within the previous 12 months had ONE of the following:

1) Nonreactive serology; or

2) Symptoms suggestive of primary or secondary syphilis; or

3) Sexual exposure involving a partner(s) with primary, secondary or early latent syphilis (4).

Note: When staging is uncertain in an asymptomatic person who within the past year had an exposure to a sexual partner(s) with unknown syphilis status, stage as early latent for reporting and contact tracing purposes (refer to Section 8.2 Management of Contacts), but treat as late latent (i.e. three weekly doses of penicillin G benzathine; see Table 2: Treatment of Syphilis).

3.5 Late Latent Syphilis (greater than one year after infection)

Lab Confirmed Case – Late Latent Syphilis

[1] Includes reinfection or treatment failure based on history and/or a four-fold or greater increase in titre over the last known non-treponemal test.

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An asymptomatic person with persistently reactive treponemal serology (regardless of nontreponemal serology reactivity) who does not meet the criteria for early latent disease and who has not been previously treated for syphilis (4).

3.6 Tertiary Syphilis

Lab Confirmed Case – Tertiary Syphilis

Reactive treponemal serology (regardless of nontreponemal test reactivity) together with characteristic late abnormalities which may involve the cardiovascular system, central nervous system, bone, skin or other structures, in the absence of other known causes of these abnormalities (*T. pallidum* is rarely seen in these lesions, although when present, is diagnostic) (4).

For more details on symptoms of tertiary syphilis, see Section 5 Clinical Presentation and Natural History.

3.7 Neurosyphilis

Neurosyphilis refers to a site of infection and is not a stage of infection. Neurosyphilis can occur at any time after initial infection and may be seen during any stage of syphilis – congenital, primary, secondary, early latent, late latent, or tertiary.

3.7.1 Early Neurosyphilis (less than one year after infection)

Fits the criteria for primary, secondary, or early latent syphilis (above) and ONE of the following:

1) Reactive Venereal Disease Research Laboratory (VDRL) test in non-bloody cerebrospinal fluid (CSF) followed by reactive treponemal specific antibodies in CSF; or

2) Clinical evidence of disease consistent with early neurosyphilis (**see Section 6.6 Neurosyphilis**) AND either elevated CSF leukocytes OR elevated CSF protein, in absence of other known causes (4).

3.7.2 Late Neurosyphilis (greater than one year after infection)

Fits the criteria for tertiary, or late latent syphilis (above) and ONE of the following:

1) Reactive VDRL in non-bloody CSF; or

2) Clinical evidence of late neurosyphilis (**see Section 6.6 Neurosyphilis**) AND either elevated CSF leukocytes or elevated CSF protein in the absence of other known causes (4).

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a. Not available in most medical laboratories including Cadham Provincial Laboratory (CPL).

b. Direct fluorescence antibody testing for syphilis is not routinely available in Manitoba but may be used in exceptional circumstances.

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c. Includes any evidence of congenital syphilis on physical examination (e.g., hepatosplenomegaly, consistent rash, condyloma lata, snuffles, pseudoparalysis), evidence of congenital syphilis on radiographs of long bones, a reactive CSF VDRL, or an elevated CSF leukocytes or protein without other cause.

d. A persistent treponemal serologic reaction at 18-24 months of age confirms the diagnosis of congenital syphilis. In this case, **change** the case classification to lab confirmed. For all other probable cases, including children who have an absent serologic reaction (both treponemal and nontreponemal tests) at, or before, 18-24 months of age, do **not** change the classification from probable.

e. Inadequate treatment consists of any non-penicillin therapy or penicillin administered during pregnancy but less than 30 days before delivery, or despite treatment there has been an inadequate drop in nontreponemal titres. Note: The type of penicillin administered is important and is usually penicillin G benzathine in pregnancy, with the exception of treatment for neurosyphilis.

f. An older child may have stigmata (e.g., interstitial keratitis, sensorineural hearing loss, anterior bowing of shins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, rhagades, or Clutton joints) (5).

4. Reporting and Other Requirements

4.1 Laboratory

All positive laboratory results for *T. pallidum* are reportable to the Manitoba Health Surveillance Unit (MHSU) by secure fax (204-948-3044).

4.2 Health Care Professional

To support Public Health investigation and to meet the requirement for contact notification under the Reporting of Diseases and Conditions Regulation in the Public Health Act, all cases and contacts are reportable by the attending health care professional to the MHSU using the following forms or by direct entry in the Public Health Information Management System (PHIMS):

The Provider Report Form for Sexually Transmitted and Blood-Borne Infections (STBBI) and STI Treatment
https://www.gov.mb.ca/health/publichealth/surveillance/docs/mhsu_6781.pdf

The Congenital Syphilis Investigation Form
https://www.gov.mb.ca/health/publichealth/surveillance/docs/mhsu_2667.pdf and user guide instructions https://www.gov.mb.ca/health/publichealth/surveillance/docs/mhsu_2667_ug.pdf.

5. Epidemiology

5.1 Reservoir

Humans.

5.2 Transmission

Approximately 90% of all syphilis is sexually transmitted. Exposure mainly occurs during anal, oral, or

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vaginal intercourse. Transmission occurs through direct contact with infectious exudates from moist skin lesions or mucus membranes of infected persons during sexual contact (1, 6). Primary, secondary, and early latent stages are considered infectious, with an estimated risk of transmission per partner of 60% (7). There is a 25% chance of relapse from early latent syphilis to secondary stage (7).

Transmission following blood transfusion, sharing of needles and drug equipment, or accidental direct inoculation (e.g., needle stick injury) is rare (7). Syphilis can be transmitted via transfusion of contaminated blood and solid organ transplantation, but is rare due to donor screening and blood processing. Ulcerative STIs like syphilis promote HIV transmission and/or acquisition by augmenting HIV infectiousness and susceptibility.

Pregnant people can transmit the infection transplacentally to the fetus at all stages of pregnancy during the course of untreated disease or during passage through the birth canal (8).

5.3 Occurrence

Infectious syphilis is on the rise in Canada, with declared syphilis outbreaks in many provinces. The number of cases of congenital syphilis has also significantly increased since 2015, in parallel to the increase observed in rates of infectious syphilis. National epidemiological reports are available at https://www.canada.ca/en/services/health/publications/diseases-conditions.html

6. Clinical Presentation and Natural History

6.1 Incubating Syphilis

Persons with incubating syphilis are asymptomatic. They are identified through self-reporting or case investigation and include those exposed to a confirmed syphilis case within the last 90 days. An early spirochetemia develops during this phase, which results in widespread secondary invasion throughout the body (3).

Note: For provincial surveillance purposes, any cases reported as “incubating” should be categorized as early latent syphilis.

6.2 Primary Syphilis

Primary syphilis most often presents as a single lesion (i.e., chancre) that develops at the site of inoculation. For a primary chancre, the incubation period is three days to three months, usually about three weeks (3). Chancres are typically painless, but some may be painful (12). The chancre is most commonly found in the anogenital area, but may occur at any site, including the mouth and fingers. The individual may be asymptomatic, and chancres that are internal (inside the vagina or anus) may go unnoticed. The chancre usually resolves spontaneously in one to four months. Painless, firm regional lymphadenopathy, often associated with genital chancres, is common and occurs in up to 80% of patients.

Variations in clinical presentation have been more commonly reported in individuals living with HIV, including multiple single chancres and chancres that may be slower to resolve (9).

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6.3 Secondary Syphilis

The secondary stage occurs 2 weeks to 6 months following exposure, and is a disseminated form of the infection which can produce a range of symptoms.

The most common feature is a **skin rash**, which is present in about 90% of cases. This rash may be macular, papular, papulosquamous, pustular, or non-specific, and typically involves the palms of the hands and soles of the feet. The rash usually resolves without scarring over several weeks.

Other symptoms include:

- Condylomata lata – painless, large fleshy lesions that are highly infectious and develop in warm moist areas such as the perineum and perianal skin, axillae, and beneath the breasts
- Constitutional symptoms such as fevers, muscle aches, headache, and weight loss
- Mucosal lesions
- Temporary alopecia or patchy hair loss

The original anal, genital, or oral chancre is still present in up to 30% of patients with secondary syphilis.

There may be evidence of central nervous system involvement such as signs and symptoms of meningitis (e.g. headaches), uveitis/retinitis (e.g. blurred vision, eye redness, flashes or floaters), or otic symptoms (e.g. hearing loss, tinnitus).

6.4 Latent Syphilis

Left untreated, secondary syphilis may progress to a period of subclinical infection where individuals are asymptomatic.

Latent syphilis is divided into early latent and late latent syphilis.

A patient with **early latent syphilis** is considered infectious, and has a 25% risk of relapse to secondary syphilis. Individuals are classified as having early latent disease if they are asymptomatic and have acquired the infection within the past year, including those who:

- have seroconverted within the past year, or,
- have had unequivocal symptoms of primary or secondary syphilis within the past year,
- have had a sexual encounter with a partner(s) with primary, secondary or early latent syphilis within the past year,
- have had a sexual encounter within the past year with a partner(s) with unknown syphilis status.

Note: When staging is uncertain in an asymptomatic person who within the past year had an exposure to a sexual partner(s) with unknown syphilis status, stage as early latent for reporting and contact tracing purposes (refer to Section 8.2 Management of Contacts), but treat as late latent (i.e. three weekly doses of penicillin G benzathine; see Table 2: Treatment of Syphilis).

Individuals are classified as having **late latent disease** if they are asymptomatic and have acquired the infection more than one year ago. Late latent syphilis is not considered infectious. However, a pregnant

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person with late latent syphilis can infect their fetus in utero.

6.5 Tertiary Syphilis

Tertiary syphilis is a slowly progressive, inflammatory disease that can affect any organ in the body and produces clinical illness 10-30 years after the initial infection. Tertiary syphilis refers to gummatous or cardiovascular syphilis, or late neurosyphilis.

6.5.1 Gummatous syphilis (late benign syphilis)

Gumma or granulomatous-like lesions are indolent and most commonly found in the skeletal system, skin, and mucous membranes, but can develop in any organ. Lesions rarely cause incapacity or death, but when lesions occur in organs like the brain or heart, serious complications occur.

6.5.2 Cardiovascular syphilis

Cardiovascular syphilis results from destruction of the elastic tissue of the aorta which leads to ascending aortitis and the formation of aneurysms that, rarely, rupture.

6.6 Neurosyphilis

Central Nervous System (CNS) disease can occur during any stage of syphilis. Consultation with an infectious disease specialist is recommended for all cases of neurosyphilis.

A patient who has clinical evidence of neurologic involvement with syphilis (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis) should have a CSF examination (10). Co-infection with HIV increases the risk of neurosyphilis. Neurosyphilis is divided into early (acute) neurosyphilis and late (chronic) neurosyphilis (3). Both early and late neurosyphilis can be asymptomatic (no signs or symptoms of CNS disease).

Early neurosyphilis occurs within the first year of infection. Symptoms of early neurosyphilis include meningitis, involvement of the eye (most commonly uveitis), hearing loss, or ischemic stroke.

Late neurosyphilis occurs more than one year after infection. Typical findings of late neurosyphilis are general paresis and tabes dorsalis. General paresis is a severe progressive deterioration of mental function, which may also include motor changes. Tabes dorsalis is a disease of the posterior columns of the spinal cord and of the dorsal roots. It most commonly presents as sensory ataxia and lancinating pains. (11)

6.7 Syphilis in Pregnancy and Congenital Syphilis

Syphilis can be transmitted transplacentally to the fetus at all stages of syphilis (9). Syphilis can also be transmitted during passage through the birth canal when the newborn infant contacts a genital lesion (8). Breastfeeding does not result in transmission of syphilis unless an infectious lesion is present on the breast. Pregnancy has no known effect on the clinical course of syphilis in the birthing parent. The rate

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of perinatal transmission in an untreated person is 70-100% in primary or secondary syphilis, 40% for early latent syphilis, and less than 10% for late latent disease in pregnancy. Spontaneous abortion, fetal demise, and late-term stillbirth occur in approximately one third of untreated early pregnancy infections.

Clinical manifestations of congenital syphilis are divided into early (appear within the first two years of life) and late (after first two years of life) stages.

Most clinical signs of **early congenital syphilis** develop within the first three months of life, usually by five weeks of age. The majority of infants with congenital syphilis are asymptomatic at birth. The most common findings in symptomatic infants include:

- snuffles or persistent rhinitis (the nasal discharge may be profuse, purulent, or blood-tinged and is highly infectious)
- hepatomegaly with or without splenomegaly
- skeletal abnormalities
- rash (often maculopapular that results in desquamation, but other presentations include bullous or ulcerative lesions, fissures, mucous patches, and condylomata lata)
- jaundice
- generalized lymphadenopathy

In addition, there may be CNS involvement, either asymptomatic or symptomatic. However, symptomatic presentation is rare, unless the infant did not receive treatment in the neonatal period. Other manifestations of early congenital syphilis have been described, but are rarely seen.

Late congenital syphilis usually manifests after two years of age with some of the clinical findings not appearing until later in childhood and rarely in adulthood. Late manifestations include Hutchinson's triad of interstitial keratitis, peg-shaped upper incisors, and eighth cranial nerve deafness. Hearing loss can be sudden and usually occurs at eight to 10 years of age.

6.8 HIV and Syphilis

HIV and syphilis coinfection is common. As with other ulcer-causing infections, syphilis can enhance the acquisition of HIV. Syphilis in individuals living with HIV can be highly aggressive, and can progress from primary to tertiary syphilis over several years.

Syphilis infection in people with HIV co-infection may present differently such as more constitutional symptoms, greater organ involvement, atypical and florid skin rashes, multiple genital ulcers, concomitant chancre during the second stage, and a significant predisposition to develop symptomatic neurosyphilis, especially uveitis, may be seen with HIV co-infection. However, these manifestations can also be seen in individuals without HIV co-infection (3).

Co-infected individuals should be managed in consultation with an infectious disease specialist or physician knowledgeable in HIV.

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7. Diagnosis of Syphilis

The diagnosis of syphilis is based on history, physical examination, and laboratory investigation.

7.1 Who to test for syphilis?

- All people who present with symptoms of syphilis such as anal, genital, or oral ulcers, generalized maculopapular rash (especially if including palms and soles) and/or lymphadenopathy
- All sexual contacts to syphilis cases
- All pregnant people (see below for details)
- All people with new, multiple, or anonymous sexual partners should be routinely tested every three to six months
- All people requesting STI testing
- All people with any confirmed or suspected STI such as gonorrhea, chlamydia or HIV
- **Consider offering STI testing to all clients/patients as part of routine care.**

7.2 Serology

Serologic tests for syphilis are essential for diagnosis of individuals, for following treatment response, and for screening purposes. They detect antibodies formed during the course of a syphilitic infection. Two tests are performed: treponemal test and non-treponemal test. Treponemal tests are necessary to establish a diagnosis of syphilis. Nontreponemal tests, such as Rapid Plasma Reagin (RPR) or VDRL, are useful for monitoring treatment response and can be useful for staging particularly in determining recent infection or reinfection. Serologic test results for syphilis, on rare occasions, may be negative in active cases, especially in older patients, or very early in primary infections. See Table 1: Interpretation of Serologic Tests for Syphilis.

There are two types of serologic screening algorithms used: traditional and reverse algorithms. The traditional algorithm uses the nontreponemal test to screen. If positive, it is followed by one or two treponemal test. The reverse algorithm, which is used in Manitoba at CPL, starts with a treponemal test to screen. If positive, it is followed by a nontreponemal test and sometimes a second confirmatory treponemal test. The second confirmatory treponemal test is usually completed when there is no history of reactive syphilis serology. However, CPL does not routinely perform a 2nd confirmatory treponemal test, but will complete it if either the first treponemal screening test is borderline positive OR the nontreponemal test is negative (in the presence of a reactive treponemal screening test).

All clinical serology testing and screening for syphilis are performed at CPL. Samples are routinely tested Monday-Friday within 24 hours of being received. Contact the Serology section at CPL at 204-945-6123 for questions about testing and 204-945-6805 to order CPL requisition forms. After hours testing is conducted for transplant and other emergent purposes. An appropriate sample is 5-10 ml of blood collected in a red-stoppered tube which should be sent to CPL with a request for “Syphilis Screen” or broader STBBI screening. The CPL lab requisition should also provide information on the reason for testing (sex partner of case, genital ulcer, clinical findings, etc.). It is extremely important to include the relevant history on the lab requisition. For prenatal screening, practitioners should check the prenatal panel box on the CPL requisition.

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Routine screening of umbilical cord blood is NOT recommended for serological testing where a diagnosis of congenital syphilis is considered. Cord blood that is contaminated with blood from the mother or birthing parent may lead to a false positive test result. Such specimens will be stored but not tested. To assess for congenital syphilis, specimens collected from both the mother or birthing parent and infant by venipuncture are recommended to provide reliable results.

In situations where maternal or birthing parent syphilis infection status is unknown (e.g., no testing done during the pregnancy), testing of maternal or birthing parent serum is preferred to testing infant serum alone because infant serum can be nonreactive if maternal or birthing parent serology is low titre or if the infection was late in pregnancy. Contact CPL if further diagnostic strategies are sought.

7.2.1 Nontreponemal Tests (VDRL and RPR)

Syphilis infection leads to the production of nonspecific antibodies (IgM and IgG) directed against a lipoidal antigen resulting from the interaction of host tissues with *T. pallidum* or from *T. pallidum* itself. This antibody-antigen reaction is the basis of nontreponemal tests such as the VDRL and the RPR. The RPR test is more sensitive than the VDRL. CPL uses both RPR (for serum specimens) and VDRL (for CSF) tests. In the situation where RPR and VDRL in serum is obtained in the same individual over time, it is important to note that the titre values obtained from these tests do not directly correlate, therefore only one of these tests should be used to monitor treatment response.

After adequate treatment of syphilis, nontreponemal tests (NTT) usually become nonreactive. However, even with sufficient treatment, patients sometimes have a persistent low-level positive NTT referred to as serofast. NTT titres of people who have been treated for latent or late stages of syphilis or who have become reinfected do not decrease as rapidly as do those of people in the early stages of their first infection. In fact, they may remain serofast for life (13).

VDRL and RPR become positive one to four weeks after the appearance of the primary chancre or six weeks after exposure. Biologic false positive reactions occur at a rate of 1-2% in the general population.

Serial NTT are useful to determine the stage of the disease; a fourfold rise in titre may indicate recent infection, immune suppression, or reinfection in an adequately treated person, or relapse in an inadequately treated person. Adequate treatment of infectious syphilis is indicated by a fourfold or greater decline in titre within one year. Titres should generally become nonreactive or weakly reactive within one year following treatment of primary syphilis and within two years after treatment for secondary syphilis. Treatment of late latent syphilis usually has little or no effect on the titre and should not be used to gauge the adequacy of the treatment. Titres tend to become lower with time after treatment of late latent syphilis, but serum frequently remains reactive, usually at a low titre. As with all quantitative serologic tests, only a fourfold or greater change in titre is meaningful. Please see Table 4: Adequate Serologic Response to gauge treatment response.

7.2.2 Specific Treponemal Tests

These tests measure antibodies against specific *T. pallidum* antigens and help confirm the diagnosis of syphilis. The specific treponemal antibody tests performed in most laboratories are treponemal-specific

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chemiluminescent microparticle immunoassay (CMIA), *T. pallidum* particle agglutination tests (TP-PA) and fluorescent treponemal antibody-absorption test (FTA-ABS).

Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. Up to 15% lose their treponemal-specific antibodies over time, particularly if they were treated early during the primary stage. Treponemal test antibody titres correlate poorly with disease activity and should not be used to assess treatment response.

False positive results can occur, especially with the FTA-ABS test, in patients with Lyme disease, HIV, pregnancy, substance use, toxoplasmosis, *Helicobacter pylori*, autoimmune disorders like lupus and rheumatoid arthritis, and in those with FTA-ABS results of < 3+ in intensity. Other spirochetal illnesses, such as relapsing fever (*Borrelia* spp.), the nonvenereal treponematoses (yaws, bejel, pinta), leptospirosis, or rat-bite fever (*Spirillum minus*), also yield positive nontreponemal and treponemal test results (3); however, the clinical and epidemiologic characteristics differentiate these infections from syphilis.

Table 1: Interpretation of Serologic Tests for Syphilis

Scenario Number	Screening Test e.g., Treponemal Specific Antibody Test (CMIA)*	NTT (VDRL/RPR)	Second (confirmatory) Treponemal Specific Antibody Test (TP-PA)	Final Syphilis Interpretation (Printed on CPL Report)	Notification to Public Health*
1	Non-Reactive	Not Done	Not Done	Cannot exclude recent infection if specimens collected within 2-3 weeks after appearance of suspect lesions.	No report
2	Reactive (No previous CMIA positive result)	Non-Reactive	Non-Reactive	Indeterminate syphilis results. The result suggests very recent infection OR a nonspecific reaction. Repeat testing should be considered after 7-10 days if clinically indicated.	No report
3	Reactive (with previous CMIA positive result)	Non-Reactive	Not Done	Indeterminate. Combined with previous test results, these findings suggest a nonspecific screening test result.	No report
4	Reactive (No previous reactive syphilis serology)	Non-Reactive	Reactive	The results suggest either recent or previous treponemal infection.	Yes

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Scenario Number	Screening Test e.g., Treponemal Specific Antibody Test (CMIA)*	NTT (VDRL/RPR)	Second (confirmatory) Treponemal Specific Antibody Test (TP-PA)	Final Syphilis Interpretation (Printed on CPL Report)	Notification to Public Health*
5	Reactive (No previous reactive syphilis serology)	Reactive	Reactive OR Not Done	The results suggest either recent or previous treponemal infection.	Yes
6	Reactive (Previous reactive syphilis serology)	Reactive	Not Done	The results suggest either recent or previous treponemal infection. This syphilis CMIA positive patient has a known history of reactive confirmatory syphilis serology. Clinical correlation is required.	Yes
7	Reactive (Previous reactive syphilis serology)	Non-Reactive	Not Done	The results suggest either recent or previous treponemal infection. This syphilis CMIA positive patient has a known history of reactive confirmatory syphilis serology. Clinical correlation is required	Yes

* Due to a technical aspect, CMIA results do not appear on the public health version of the syphilis results. However, to aid the interpretation by public health, scenarios 6 and 7 contain a comment within the interpretation indicating the individual was found to have a positive CMIA result. Also note that TP-PA and VDRL/RPR are not done in the case of a negative CMIA. Therefore, one can assume the CMIA was positive if a report is received with a positive TP-PA and/or VDRL/RPR.

*Previous CMIA positive result refers to a previous sample with a positive syphilis CMIA, but negative or indeterminate TP-PA and the CMIA on this current sample is static as compared to the previous sample.

Table Notes and Abbreviations:
TP-PA: used as a second confirmatory test when there is no previous positive test and either the screening test (CMIA) is borderline positive or the RPR is negative.

NOTES:
- The ordering practitioner will receive all results; however, public health notification is received only for the latter four result scenarios detailed in Table 1 above. Upon request, Public Health may receive

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other results as deemed necessary. If syphilis PCR is positive, then it overrides any serologic results or interpretation in terms of diagnosis.
- Result scenarios 4-7 in Table 1 are referred to regional public health (region of case residence) for follow-up. Details about case and contact management are outlined in this protocol.
- Questions regarding interpretation of testing results should be directed to CPL.

7.3 Direct Tests from Lesions

7.3.1 Nucleic Acid Amplification Test (NAAT)

CPL requests a dacron swab (e.g.: swab from GenProbe package) be collected from suggestive mucocutaneous lesions (chancres, mucous patches, moistened condyloma latum or newborn nasal discharge) for NAAT (e.g., PCR), and placed in viral transport medium. NAAT is used for definitive syphilis diagnosis as well as for subtyping. Prior arrangements with the lab are generally not required. These samples must remain refrigerated until sent to CPL and the CPL requisition should clearly indicate the site and test requested: *T. pallidum* or syphilis PCR testing.

7.3.2 Dark-field Microscopy and Direct or Indirect Fluorescent Antibody Test (DFA or IFA)

Dark-field microscopy, DFA and IFA testing are techniques that are not routinely available in most medical labs including CPL. They are often not practical tests because specimens must be appropriately collected and quickly examined within five to 20 minutes of collection. However, when performed on specimens from lesion exudates or tissues when an active chancre, mucous patch, or condyloma latum is present, are the classic methods for diagnosing early syphilis. As well, it is useful for testing nasal discharge in a neonate with snuffles.

7.4 Cerebrospinal Fluid (CSF) Testing for Neurosyphilis

In patients with suspected/confirmed syphilis, indications for CSF examination typically via lumbar puncture include the following:

- Congenital syphilis;
- Presence of neurologic, ophthalmic or otic signs or symptoms;
- Tertiary syphilis;
- Previously treated patients who fail to achieve an adequate serologic response to treatment;
- Patients with HIV co-infection with RPR ≥1:32 dilutions and CD4 ≤350 cells/μL(7)

The recommended syphilis tests for CSF are VDRL, FTA-ABS and sometimes syphilis PCR. The diagnosis of neurosyphilis is usually made on a combination of reactive serologic results, abnormalities of CSF cell count or protein or a reactive CSF VDRL with or without clinical manifestations (7).

Note: The CSF FTA-ABS is reported by the lab even if the CSF VDRL is non-reactive. CSF FTA-ABS is more sensitive but less specific than the VDRL. When the FTA-ABS is the only positive CSF test, the diagnosis of neurosyphilis should be interpreted within the context of the clinical scenario. Consultation with an infectious disease specialist and/or the laboratory is recommended.

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There may be situations where an individual who is a confirmed case of syphilis has clinical findings which are consistent with neurosyphilis and it is practically not feasible due to geographic location or other reasons to obtain a CSF sample. In this case, it may be reasonable, in consultation with an infectious diseases specialist, to treat for neurosyphilis without obtaining the CSF sample.

7.5 Tests for Pregnant People and Newborn Infants

Screen ALL pregnant people for syphilis three times during pregnancy. This screening should be done regardless of any previous syphilis test result. The first test should be done within **the first trimester** (in addition to testing for HIV, Hepatitis B (HBV), gonorrhea, and chlamydia; Hepatitis C testing should be done if indicated). ALL pregnant people should be screened again at **28-32 weeks** gestation and again **at delivery**.

Note: More frequent re-screening may be indicated during pregnancy if there are ongoing identified risks. This may include but is not limited to, presenting with symptoms concerning for STBBI, positive test of another STBBI during pregnancy, disclosure of new, multiple, or anonymous sexual partners, or sexual contact with someone with symptoms of or who has tested positive for STBBI.

In addition, ALL pregnant people should be tested monthly for syphilis during pregnancy and again at delivery if:

- they are newly diagnosed with syphilis infection or reinfection during the pregnancy; or
- had a previous syphilis infection, but received or is receiving treatment during the current pregnancy.

Paired maternal/birthing parent-infant syphilis serology should be sent in the immediate post-partum period for ALL infants born to mothers or birthing parents with reactive syphilis serology, regardless if the infection was prior to or during the current pregnancy. The specimens for the mother or birthing parent and infant do not need to be drawn at the exact same time, but should be drawn as closely together and no longer than within a week of each other. Infant samples should be from venipuncture and not from the umbilical cord. The syphilis testing should be sent as STAT. Following this, a non-urgent consultation with Pediatric Infectious Diseases (204-787-2071) is recommended to determine whether any further investigation or treatment is required for the newborn prior to discharge as well as follow-up testing. Consultation with a pediatric infectious diseases specialist prior to the infant's discharge is particularly recommended for infants born to a person who was newly diagnosed with syphilis infection/reinfection during the pregnancy or received treatment for syphilis infection during the pregnancy. Newborns should not be discharged from hospital prior to confirming that syphilis serology has been sent for the mother/birthing parent-infant pair. All positive results require follow-up.

Interpretation of reactive antibodies in the neonate must take into consideration the maternal/birthing parent history, including stage of syphilis, history of treatment, and syphilis serology results.

Infants presenting with signs or symptoms compatible with congenital syphilis should be tested for syphilis even if the mother or birthing parent was seronegative at delivery, as they may have been incubating at the time of delivery (7).

Pregnant people delivering a hydropic or stillborn infant at ≥20 weeks gestation should be screened for syphilis (7). Additionally, placenta and neonatal nasal discharge and/or skin lesions may

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be examined by NAAT for *T. pallidum*.

Consultation with a pediatric infectious diseases specialist is strongly recommended for all infants who are being considered for evaluation and treatment of congenital syphilis. Investigations for these infants should include syphilis serology, CSF examination, NP swab for syphilis PCR and long bone x-rays.

8. Control

8.1 Management of Cases

It is essential that the stage of syphilis be accurately assessed and documented in order to ensure appropriate management of cases and contacts.

- Close collaboration between Public Health and Primary Care, in addition to timely completion and return of case and contact investigation forms, are essential to ensure there is sufficient information to identify and locate contacts.

- Evaluation of seroreactive persons should include a history and physical examination, laboratory testing, risk assessment, and promotion of safer sex practices.

- All persons with syphilis should be counseled concerning the risks of infection with HIV and other STBBIs and testing for these infections should be performed. Genital ulcers should also be tested for herpes simplex virus and/or chancroid and/or lymphogranuloma venereum, depending upon epidemiologic risk (7).

- Offer vaccination for hepatitis A (HAV), hepatitis B (HBV), human papillomavirus (HPV), or others (e.g., monkey pox) if appropriate (7).

- Cases with infectious syphilis (primary, secondary, and early latent) should be interviewed for sex contacts (see Section 7.2 Management of Sexual Contacts (Partner Notification) and Perinatal Contacts).

- People with infectious syphilis should be advised to avoid all sexual contact (including oral sex) until 7 days after the completion of treatment and the resolution of infectious lesions, whichever is greater (14). If any sexual contact occurs during this period, condoms should be used. They should also be advised to avoid sexual contact with any ongoing partners until the partners have sought medical evaluation and/or completed treatment for possible infection.

- Monitor clinical and serological response (refer to Table 3: Recommended Nontreponemal Testing (NTT) Following Treatment and Table 4: Adequate Serologic Response).

- Hospitalized cases should be managed with appropriate infection prevention and control precautions. Refer to Manitoba Health's Routine Practices and Additional Precautions: Preventing the Transmission of Infection in Health Care available at: www.gov.mb.ca/health/publichealth/cdc/docs/ipc/rpap.pdf.

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8.2 Who to Treat for Syphilis without Test Results

ALL of the following people (pregnant or not) should receive treatment for syphilis with penicillin G benzathine (Bicillin-LA®) administered intramuscularly (IM), without awaiting syphilis serology results (e.g., test and treat at the same time):

- any person who presents with symptoms of primary or secondary syphilis (such as anal, genital or oral ulcers or skin rash involving palms or soles);
- any person who is a direct contact of a person with confirmed primary, secondary or early latent syphilis; and
- at the clinician's discretion, an asymptomatic person who is screened for syphilis who is considered at high risk of being infected (i.e., sex contact of a person with confirmed syphilis; person who injects drugs; person who has multiple sex partners) and who is not likely to return for follow-up.

8.3 Treatment of Cases and Contacts

Refer to Table 2: Treatment of Syphilis for the specific treatment of syphilis by stage. Tables 4 and 5 provide recommendations for timing of follow-up serology and adequate serologic response respectively. Additional resources include the current Public Health Agency of Canada's Canadian Guidelines on Sexually Transmitted Infections www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/section-5-10-eng.php.

It is recommended that syphilis serology be drawn on the same day of treatment, or as soon as possible afterwards if it has not been done in the seven days prior to treatment. This is important to determine the peak titre in order to gauge treatment response.

Consider consultation with an infectious diseases specialist for any complicated cases, all cases of neurosyphilis, or if additional assistance required.

8.3.1 First Line Therapy

Penicillin G benzathine (Bicillin-LA®) administered IM is the preferred drug for treatment of all stages of adult syphilis not involving the CNS (7). The short-acting benzyl penicillin formulation of penicillin G is not adequate for achieving cure and should not be used (7).

Aqueous crystalline penicillin G administered intravenously (IV) is preferred for neurosyphilis (7) as treponemicidal levels of penicillin G benzathine are not reliably achieved in the CSF (3).

Penicillin desensitization is the only option for the treatment of syphilis in pregnant people with a penicillin allergy, as ceftriaxone and doxycycline cannot be used.

8.3.2 Second line therapy

Ceftriaxone IV/IM is recommended as second line therapy for the treatment of syphilis only in **non-**

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pregnant people who are allergic to penicillin and unable to access penicillin desensitization.

8.3.3 Third Line Therapy

Doxycycline is recommended as a third line therapy for the treatment of syphilis only in **non-pregnant** people who are allergic to penicillin and who are unable to receive ceftriaxone or penicillin desensitization.

Note: Azithromycin is no longer recommended as an alternate treatment for syphilis under any circumstances.

Note: Therapeutic regimens other than penicillin have not been well studied, especially in patients with syphilis of longer than one year's duration; therefore, careful follow-up is mandatory if other regimens have been used. Consultation with an infectious diseases specialist is advised if regimens other than penicillin are considered.

8.3.4 Ordering STI Medications

STI medications are available free of charge and can be ordered by completing and faxing the STI Medication Order Form available at: www.gov.mb.ca/health/publichealth/cdc/protocol/form11.pdf as per instructions on the form.

8.3.5 How to Administer Penicillin G Benzathine

For adults, treatment with penicillin G benzathine includes two injections of 1.2 million units each administered IM in a single session (i.e., total of 2.4 million units). The penicillin G benzathine in preloaded syringes is provided free of charge by Manitoba Health (see order form above). The product monograph will be provided with the penicillin G benzathine (Bicillin-LA®) medication in 2 ml TUBEX sterile cartridge-needle units containing 1.2 million units of benzathine penicillin G. The dosage, administration, contraindications, and precautions sections should be reviewed thoroughly prior to use. www.pfizer.ca/sites/default/files/202004/Bicillin_PM_E_234892_08Apr2020.pdf

The ventrogluteal site is the typical location for IM administration of penicillin G benzathine. For instructions on administration into the ventrogluteal site please see https://albertahealthservices.ca/assets/info/hp/srh/if-hp-srh-administering-bicillin-l-a-ventrogluteal.pdf

8.3.6 Jarisch-Herxheimer Reaction

Jarish-Herxheimer reaction is a reaction to endotoxins released by the death of microorganisms within the body. It presents as an acute febrile illness with headache, myalgia, and chills/rigors that can occur as early as two hours after antimicrobial treatment, with resolution within 24 hours (7). Patients should be made aware of this possible reaction to treatment especially with penicillin (7). The reaction is more common in secondary syphilis (70-90%), but can occur at any stage of infection (7).

In general, the reaction is not clinically significant unless there is neurologic or ophthalmologic involvement, or in pregnancy where it may cause fetal distress and premature labour - see section 8.3.10

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Syphilis in Pregnancy for further information (7).

Patients demonstrating a reaction can be treated with antipyretics. More severe reactions can be treated with corticosteroids in consultation with a medical specialist (7).

8.3.7 Missed or Delayed Doses during the Treatment of Late Latent Syphilis

The recommended treatment for late latent syphilis is three weekly doses of penicillin G benzathine. For non-pregnant people, an interval of 10-14 days between doses of penicillin G benzathine may be acceptable before restarting the series of injections. However, for pregnant people receiving a three-dose course of penicillin G benzathine treatment, delay in doses is not optimal, so if there is a delay of greater than nine days between doses, the series of injections should be restarted. This is based on pharmacologic considerations that an interval of seven to nine days may be preferred (20).

8.3.8 Retreatment

Retreatment should be considered, including during pregnancy when:

- clinical signs or symptoms of syphilis persist or recur;
- there is a fourfold increase in NTT titre;
- a NTT with a high titre initially fails to show adequate decrease following treatment (7, 14); or
- there is a history of recent sexual exposure to a person with infectious syphilis (7).

For people who are being retreated because of possible treatment failure (e.g., inadequate serologic response), they should receive additional neurologic examinations and reevaluation for HIV infection in addition to clinical and serologic follow-up. They should be retreated according to the schedules recommended for syphilis of more than one year's duration (i.e., three weekly doses of penicillin G benzathine). In general, a person should be retreated only once as they may maintain stable, low NTT titres. Consider consultation with an infectious diseases specialist to review the management of these cases.

8.3.9 Syphilis in People Living with HIV

People co-infected with HIV may require a longer course of treatment, as well as closer and longer follow-up (7). Consultation with an infectious diseases specialist or physician knowledgeable in HIV is strongly recommended.

8.3.10 Syphilis in Pregnancy

All pregnant people newly diagnosed with syphilis during pregnancy should receive prompt treatment appropriate to their stage of disease (7). Refer to Table 2 for treatment recommendations and Tables 4 and 5 for NTT and treatment response follow-up.

Despite the administration of the recommended penicillin regimen, as many as 14% of pregnant people diagnosed with syphilis in late pregnancy will have fetal deaths or deliver infants with clinical evidence of

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congenital syphilis (7). Some experts recommend that pregnant people with primary, secondary and early latent syphilis (due to difficulty in accurately staging cases and potentially pregnancy related altered pharmacokinetics of penicillin) receive two doses of penicillin G benzathine 2.4 million units IM one week apart (7). The effect of this regimen in preventing fetal syphilis is not known (7), but is recommended when possible.

In pregnancy, penicillin G benzathine is the only recommended treatment for syphilis. Pregnant people who report an allergy to penicillin should be referred to the Pregnancy Penicillin Allergy De-labelling Clinic at HSC Women's Prenatal Allergy Clinic, Fax: 204-787-2876 and page the allergist on call (HSC paging 204-787-2071), where they will be seen in an expeditious way. Assessment of allergy history, appropriateness for skin-testing and/or need for penicillin desensitization during pregnancy is arranged through this clinic.

For treatment of pregnant people greater than 20 weeks gestation, obstetrical consultation is not required in every case and outpatient treatment with penicillin should not be delayed. An urgent fetal ultrasound should also be requested at the time of treatment to assess for sonographic signs of fetal syphilis (e.g., hepatomegaly, ascites and hydrops). These findings may indicate a greater risk for fetal treatment failure and such cases should be referred to an obstetrician for further consultation. However, timing and/or availability of fetal ultrasound should not delay the pregnant person's treatment.

Jarisch-Herxheimer reaction in pregnancy

In pregnant persons, Jarish-Herxheimer reaction can be associated with uterine contractions and variable deceleration in fetal heart rate but usually resolves without incident (7, 16) – see section 8.3.6 Jarisch-Herxheimer Reaction for further information. All pregnant individuals receiving treatment should be advised that if they develop signs/symptoms of a Jarisch-Herxheimer reaction (e.g., fever, decreased fetal movement, regular uterine contractions, dizziness, headache, flushing or exacerbation of skin lesions (if present)) following treatment to return to care.

8.3.11 Treatment of Congenital Syphilis

Paired maternal/birthing parent-infant syphilis serology should be sent in the immediate post-partum period for **ALL** infants born to mothers or birthing parents with reactive syphilis serology, regardless if the infection was prior to or during the current pregnancy. Non-urgent consultation with a pediatric infectious diseases specialist is recommended to determine whether any further investigation or treatment is required for the newborn prior to discharge as well as follow-up testing. Consultation is particularly recommended for infants born to a person who was newly diagnosed with syphilis infection/reinfection during the pregnancy or received treatment for syphilis infection during the pregnancy.

Consultation is strongly recommended for all infants who are being considered for evaluation and treatment of congenital syphilis. Infants with suspected congenital syphilis require intravenous treatment with penicillin G.

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8.3.12 Syphilis in Children

Although congenital syphilis, if not treated early, can present in later childhood, sexual abuse must be considered when syphilis is found in children beyond the neonatal period (7). Consultation with experts for the reporting, referral and management of such cases should be sought. Refer to Reporting of Child Protection and Child Abuse: Handbook and Protocols for Manitoba Service Providers available at:

https://gov.mb.ca/fs/childfam/pubs/handbook_child_protection_and_child_abuse.pdf?msclkid=2fd5bf08aade11ecbd9ac05794001bde.

Table 2: Treatment of Syphilis

Stage	Preferred Treatment[g]	Alternative Treatment for Penicillin-allergic Patients[i]
Non-pregnant Adults with: • Primary syphilis • Secondary syphilis • Early latent syphilis (<1 year duration)	Penicillin G benzathine 2.4 million units IM as a single dose[h]	Consider penicillin desensitization Only if penicillin allergy, unable to access penicillin desensitization, and can ensure close follow-up: Second Line: • Ceftriaxone 1g IV or IM daily for 10 days Third Line: • Doxycycline 100 mg PO BID for 14 days
Pregnant People with: • Primary • Secondary • Early latent (<1 year duration)	Penicillin G benzathine 2.4 million units IM weekly for 1-2 doses[h, k]	There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy. Insufficient data exist to recommend ceftriaxone in pregnancy. Strongly consider penicillin desensitization followed by treatment with penicillin.
Children and Adolescents with: • Primary syphilis • Secondary syphilis • Early latent syphilis (<1 year duration)	Penicillin G benzathine 50,000 units/kg/dose IM given as a single dose; maximum 2.4 million units/dose If weight is ≥40 kg, use 2.4 million units/dose. Children weighing <40 kg, require the above weight-based dosing and require pharmacy to assist with subdividing the syringe.	Consider penicillin desensitization In exceptional circumstances and when close follow-up is assured: • Ceftriaxone 1g IV or IM daily for 10 days

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Stage	Preferred Treatment[g]	Alternative Treatment for Penicillin-allergic Patients[i]
Congenital Syphilis	Crystalline penicillin G 50,000 units/kg/dose IV Dosing frequency is age dependent: • every 12 hours during the first 7 days of life, • every 8 hours for infants 8-28 days of age, • and every 6 hours for infants older than 28 days of age. Total duration, regardless of age, is 10 days. Stable IV access required. If >24 hours of therapy is missed, the entire 10 days should be restarted.	Penicillin desensitization
Non-pregnant Adults with: • Late latent syphilis (>1 year duration) • Latent syphilis of unknown duration • Tertiary syphilis not involving the CNS (e.g., cardiovascular or gummatous syphilis)	Penicillin G benzathine 2.4 million units IM weekly for 3 doses For non-pregnant people, an interval of 10-14 days between doses of penicillin G benzathine may be acceptable before restarting the series of injections.	Consider penicillin desensitization Only if penicillin allergy, unable to access penicillin desensitization, and can ensure close follow-up: Second Line: • Ceftriaxone 1g IV or IM daily for 10 days Third Line: • Doxycycline 100 mg PO BID for 28 days
Pregnant People • Late latent syphilis (>1 year duration) • Latent syphilis of unknown duration (staged as early latent and receiving a three-dose course) • Tertiary syphilis not involving the CNS (e.g., cardiovascular or gummatous syphilis)	Penicillin G benzathine 2.4 million units IM weekly for 3 doses For pregnant people, delay in doses is not optimal, so if there is a delay of greater than nine days between doses, the series of injections should be restarted.	There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy. Insufficient data exist to recommend ceftriaxone in pregnancy. Strongly consider penicillin desensitization followed by treatment with penicillin.

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Stage	Preferred Treatment[g]	Alternative Treatment for Penicillin-allergic Patients[i]
Children and Adolescents with: • Late latent syphilis (>1 year duration) • Latent syphilis of unknown duration • Tertiary syphilis not involving the CNS (e.g., cardiovascular or gummatous syphilis)	Penicillin G benzathine 50,000 units/kg/dose IM weekly for 3 doses; maximum 2.4 million units/dose If weight is ≥40 kg, use 2.4 million units/dose. Children weighing <40 kg, require the above weight-based dosing and require pharmacy to assist with subdividing the syringe.	Consider penicillin desensitization In exceptional circumstances and when close follow-up is assured: • Ceftriaxone 1g IV or IM daily for 10 days
Adults with Neurosyphilis (including presentations of ocular and otosyphilis) *Consult Infectious Diseases for all cases of Neurosyphilis	Aqueous crystalline penicillin G 3-4 million units IV every 4 hours for 10-14 days	Strongly consider penicillin desensitization If can ensure close follow-up: • Ceftriaxone 2 g IV/IM daily x 10-14 days • Other alternative treatment regimens are available, but should be administered in consultation with an infectious diseases specialist.
Epidemiological treatment of sexual contacts in the preceding 90 days to primary, secondary and early latent syphilis[j]	Penicillin G benzathine 2.4 million units IM as a single dose	

g. Reports from some jurisdictions have indicated inappropriate use of short-acting benzyl penicillin (penicillin G) IM for the treatment of infectious syphilis rather than long-acting penicillin G benzathine (Bicillin-LA). Practitioners, pharmacists and purchasing agents should be aware of the similar names of these two products to prevent and avoid inappropriate and inadequate treatment. Long-acting benzathine penicillin achieves detectable serum levels of penicillin for two to four weeks in non-pregnant adults and is required to adequately treat infectious syphilis; short-acting penicillin agents are not adequate for achieving cure.

h. Some experts recommend three weekly doses (total of 7.2 million units) of penicillin G benzathine in individuals living with HIV (7).

i. The efficacy data supporting the use of these alternative treatment agents is limited, and as such they should only be used in exceptional circumstances and when close patient follow-up is assured.

j. If a sexual contact is unreliable or unable to test, then epidemiological treatment should be strongly considered.

k. Given the complexity of accurately staging early syphilis and potentially pregnancy related altered pharmacokinetics of penicillin, some experts recommend that primary, secondary and early latent cases in pregnancy be treated with two doses of penicillin G benzathine 2.4 million units IM one week apart. The efficacy of this regimen in preventing fetal syphilis is not known, but is recommended when possible.

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8.4 Follow-up and Serologic Response to Treatment

The adequacy of therapy can be determined with serial RPR (or VDRL) tests; the same test in the same laboratory should be followed sequentially. Refer to Table 3 for recommended frequency of follow-up serological testing.

Once treatment has been completed, serological response can be used to evaluate adequacy of treatment. The guidelines for determining adequate serologic response are found in Table 4: Adequate Serologic Response.

Table 3: Recommended Nontreponemal Testing (NTT) Following Treatment (7)

Stage	Recommendations for Follow Up Nontreponemal Testing
Primary, secondary and early latent	(*), 3, 6, 12 months after treatment
Late latent and tertiary without CNS involvement (e.g., cardiovascular or gummatous syphilis)	12 and 24 months after treatment
Neurosyphilis	Patients with CSF abnormalities may require follow-up CSF testing. Follow up to be determined based on consultation with an infectious diseases specialist.
Syphilis in pregnancy	Test monthly during pregnancy and again at delivery if: • New diagnosis of syphilis infection or reinfection during the pregnancy; or • Had a previous syphilis infection, but received or is receiving treatment during the current pregnancy Note: more frequent re-screening may be indicated during pregnancy if there are ongoing identified risks for re-infection
HIV-infected (any stage)	(*), 3, 6, 12, 24 months after treatment and yearly thereafter
Congenital syphilis	Consultation with Pediatric Infectious Diseases is recommended. Infants treated for possible congenital syphilis should have serology repeated every 2-3 months up until 6 months of age, and then at 12 and 18 months of age. If syphilis serology becomes non-reactive (treponemal and nontreponemal), no further repeat serology is required. Infants with CSF abnormalities do not typically require follow-up CSF testing as long as their follow-up nontreponemal serologic titres are responding as expected.

Some experts recommend follow-up testing at one month after treatment as an additional reference point to monitor treatment response.

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Table 4: Adequate Serologic Response (7)

Following treatment of	One would expect to see
Primary syphilis	4-fold drop* at 6 months 8-fold drop at 12 months 16-fold drop at 24 months
Secondary syphilis	8-fold at 6 months 16-fold drop at 12 months
Early latent syphilis	4-fold drop at 12 months
Late latent syphilis	Treatment of late latent syphilis usually has little or no effect on the titre and should not be used to gauge the adequacy of the treatment.

* A four-fold drop = 2-tube drop (e.g., change from 1:32 dilutions to 1:8 dilutions). When calculating the change in dilutions, divide the "dilutions" by the "fold", i.e. to calculate a four-fold drop from 1:32, take 32 and divide by four, which is eight, meaning you are looking for the titre to drop to 1:8.

Notes:

- NTT may revert to nonreactive after treatment or remain at a low steady level (e.g., ≤1:4 dilutions; however, dilutions may vary) (7). Repeat testing is not required if the baseline or follow-up NTT becomes nonreactive, but may be considered in HIV-infected individuals or in recent exposures to syphilis (e.g., early primary syphilis).
- While there are no universally accepted criteria for defining treatment failure or reinfection, a rising NTT after treatment may indicate treatment failure or reinfection (7). If treatment failure is suspected, further investigation, including CSF examination may be indicated (7).
- CSF lab parameters may normalize more slowly in patients co-infected with HIV (7).
- If titres do not decrease as per the above table, repeat HIV testing and consult an Infectious Diseases specialist.

8.5 Management of Sexual Contacts (Partner Notification) and Perinatal Contacts

Rapid identification and investigation of sexual partners/contacts is essential to locate persons with early (primary, secondary, early latent) syphilis and provide them with treatment to prevent further transmission. Regulations under the Public Health Act require health care professionals to report all sexual contacts to Manitoba Health. Please use the following form to report contacts: https://www.gov.mb.ca/health/publichealth/surveillance/docs/mhsu_6781.pdf

All sexual and perinatal contacts identified within the following time periods should be located, tested, and treated if serologically reactive as per Section 8.1 Management of Cases.

The length of time for the trace-back period should be extended:

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- To include additional time up to the date of treatment;
- If the index case states that there were no sexual partners during the recommended trace-back period, then the last sexual partner/contact should be notified.
- If all partners/contacts traced (according to recommended trace-back period) test negative, then the partner/contact prior to the trace-back period should be notified (7).

Presumptive or epidemiologic treatment of sexual partners/contacts should be considered under the following circumstances (refer to Table 2 for treatment recommendations):

- Persons who were exposed within three months preceding the diagnosis of primary, secondary or early latent syphilis in a sexual partner/contact might be infected, even if testing indicates treponemal seronegative status; therefore such persons should be treated presumptively.
- Persons who were exposed more than three months preceding the diagnosis of primary, secondary or early latent syphilis in a sexual partner/contact should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.

Table 5: Trace Back Period

Patient's Stage of Syphilis	Trace-back Period*
Primary syphilis	Three months
Secondary syphilis	Six months
Early latent	One year
Late latent/tertiary	Assess long-term sexual partners/contacts and children as appropriate; the decision to test these individuals depends on estimated duration of infection in source case.
Congenital	Assess mother/birthing parent and their sexual partner(s)/contacts.

*Trace-back period refers to the time period prior to case's symptom onset or date of specimen collection (if asymptomatic)

8.6 Preventive Measures

- Education on facts about the disease and how it is transmitted (7).
- Education on risk reduction (e.g., reducing the number of sexual partners/contacts and proper and consistent use of barrier methods) (7).
- Routine screening, including the importance of regular screening during pregnancy.
- Contact tracing for all cases of infectious syphilis.
- Canadian Blood Services screens blood, organ and tissue donors for syphilis and will exclude those testing positive. Donors are notified of the positive test results and positive results are also

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reported to Manitoba Health. In addition, individuals who are known to be positive for syphilis are excluded from donating blood for at least 12 months following treatment.

9. Key Investigations Components for Public Health Response

Contact the testing provider prior to connecting with the client. All cases should be followed-up by public health to complete the public health investigation.

Key components of the case investigation include:

- Classification and staging of the case, including classification dates.
- Follow-up testing, including other STBBIs
- Recommendation/administration and documentation of treatment provided
- Monitor clinical and serologic response to treatment (refer to Tables 4 and 5).
- Immunization for HAV/HBV/HPV or others (e.g., monkey pox) if indicated
- Identification of contacts that require follow-up
- Harm reduction education/supplies if indicated
- Facilitate referral to or consultation with Infectious Diseases if required
- Education on preventive measures and/or connection to resources to support equitable health outcomes

Key components of the contact investigation include:

- Follow-up testing, including other STBBIs
- Recommendation/administration and documentation of epi-treatment provided
- Immunization for HAV/HBV/HPV or others (e.g., monkey pox) if indicated
- Harm reduction education/supplies if indicated
- Education on preventive measures

10. Documentation Guidelines and Resources

Critical data elements to collect on all cases and contacts are listed with a star (*) on the Investigation Forms.

PHIMS Quick Reference and User Guides are available at https://phimsmb.ca/.

The following is intended to provide broad guidance and timelines for the majority of syphilis case investigations, but may not align with the chronology or flow of some investigations.

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Table 6: Timelines for Documenting Syphilis Cases (Excluding Congenital Syphilis Cases) in PHIMS

Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
Region receives new Investigation from MHSU or other source. Responsible Org and Workgroup assigned by MHSU	Assign Primary Investigator or CD Coordinator Connect with MHSU if investigation referred from other source. Investigation created.	1 Day
Primary investigator/CD Coordinator reviews investigation and lab results	Update Classification and classification date Update Disposition from Pending (e.g., Follow up in Progress) If other new STBBI co-infections should be bundled together in an investigation, see PHIMS process for Co-Infections on pg. 19 of User Guide of Completion of Surveillance Forms for Reportable Diseases and PHIMS QRC 7.5a, Add an Additional Disease to an Investigation.	3 Days
Enter information received on the STBBI Provider Report Form. Send reminder to testing practitioner if form not received. Includes: • Symptoms • Stage • Site of presentation • Pregnancy • Treatment provided or plan	Update PHIMS data with information available Enter contact investigations (identified either by testing practitioner or contact with client) Author note. Upload relevant context documents per QRC 7.16 as required (e.g., personal health information/correspondence sent to public health from an outside care provider, personalized letters). Document additional presentations (e.g., neurosyphilis, cardiovascular) in PHIMS Disease Event History under Site(s). Non-critical fields (method of detection, symptoms and risk factors) should be documented whenever possible. **Document treatment as soon as confirmed.**	1-2 Weeks (may request testing practitioner to fill out STBBI Provider Form immediately for highest priority cases: e.g., prenatal)

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Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
Attempt to contact case directly if required (e.g., for additional information, contact interview, facilitate follow up testing and/or care)	After contact/attempt with testing practitioner	1-3 weeks
Follow up to complete critical data elements listed on Public Health Case Form	Complete PHIMS documentation • Includes classification and staging – *all cases should be staged by 4 weeks* – as consistent with the client's condition at the time of initial test. If insufficient information to stage case by 4 weeks, enter 'unknown' stage as placeholder. • For cases that are staged as "early latent" but are recommended to have 3 doses of benzathine penicillin G due to uncertain history of exposure, **add Intervention for treatment: Subtype – Additional Treatment Recommended**. • All treatment reported to PH on the STBBI Provider Form should be transcribed into the syphilis case investigation. The treatment course on the Provider Form investigation should be updated to "duplicate" once the medication has been entered. If unable to locate client and/or unable to meet basic care criteria (client not notified of result, no treatment provided) – hold open for at least 6 months with periodic attempts to locate, reconnect with testing practitioner. Disposition: Unable to Locate, OR Lost to Follow up. Status **open** for 6 months or more. • **Pregnant cases kept open until delivery. Once infant born create a Transmission Event and link the infant as a contact.**	4 weeks for staging and classification

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Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
For high-priority cases (e.g., persons living with HIV, pregnant persons, persons treated with second-line or third-line medications) hold open for 3 months post treatment to monitor serological response (refer to Tables 4 and 5).	Update Disposition: Hold for test results Refer to tables 4 and 5 Other cases can be closed as soon as first of Bicillin is provided. If public health is the testing and treating provider, keep open until full treatment course has been completed and plan in place for follow-up.	Up to 3 months past treatment date
Close investigation: when investigation complete.	Disposition: Follow up Complete OR Lost to Follow up, OR Unable to Locate. Investigation Status: Closed. Staging = unknown or undetermined (unable to locate or lost to follow-up is the only situation where this should be utilized, and only if there was not enough information to stage the case)	4 weeks – 6+ months
Receipt of follow up serologic results	Investigation should be re-opened if serology cannot rule out treatment failure or reinfection, (e.g. two-year gap in serologic follow up). If serology is suggestive of treatment failure, follow-up with health care provider with protocol recommendations for assessment and re-treatment. Public health does not require active follow up of suspected treatment failure once health care provider notified, except if client is pregnant. The provider should report any additional treatment provided on a new STBBI Provider Report Form.	
Quality Assurance	Each region employs a Quality Assurance process (Classification, Staging, Disposition, and Treatment). Consider use of PHIMS Quality Assurance report if PHNs working in specialized STBBI Role	6 weeks post investigation closure

Unknown contacts (those whose identity cannot be confirmed) documented in PHIMS (Transmission Event Disposition Details) do not have the same options for data entry as PHIMS contact investigations. Follow the same basic investigation steps until two unique identifiers confirmed and the contact is converted to a known client.

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Table 7: Timelines for Documenting Syphilis Contacts in PHIMS

Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
Region receives or creates a new Investigation	Assign Primary Investigator, Responsible Organization, and Workgroup. *Note that contacts entered in co-infection investigations will automatically be created as contacts to all infections of the case. If one or more diseases are not relevant to the contact follow up, delete the irrelevant disease(s) from the contact disease summary.*	1 Day
Primary investigator attempts to locate and contact client for notification of exposure	Update Disposition: Follow up in Progress	3 Days
Document testing and/or epi-treatment provided.	Update PHIMS data. Author note.	1-2 weeks
Critical data elements listed on form	Complete PHIMS documentation as soon as available If contact tests positive, close contact investigation with **Disposition: Contact Turned Case.** Continue documentation in Case Investigation. If unable to locate client and/or unable to meet basic care criteria (client not notified of exposure, no treatment provided) – hold open for up to 6 months with periodic attempts to locate, reconnect with testing practitioner. • Disposition: Unable to Locate, OR Lost to Follow up. Status open for 6 months or more. High priority contacts may be pursued for up to a year (e.g., pregnant, confirmed exposure with primary or secondary case, person living with HIV)	2 weeks up to 1 year to notify and support/ confirm testing and treatment as indicated

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Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
Close investigation when investigation complete (contact, notified, tested, and epi-treated if indicated) Close if unable to complete (e.g., lost to follow up) *See protocol section 7.2 Management of Sexual Contacts and Perinatal Contacts*	Disposition: Follow up Complete, OR, Lost to Follow Up/Unable to Locate. Status Closed.	2 weeks to 1 year
Quality Assurance	CD Coordinator Review by Quality Assurance Report level for minimal data elements only (Disposition, Treatment)	6 weeks post closure of investigation

Table 8: Timelines for Documenting Congenital Syphilis Cases in PHIMS

Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
Region receives new Investigation from MHSU. Responsible Org and Workgroup assigned by MHSU	Assign Primary Investigator or CD Coordinator	1 Day
Primary Investigator or CD Coordinator reviews investigation and lab results	Update Disposition from Pending (e.g., Follow up in Progress) Classification should remain as "Person Under Investigation" until classified and staged by 4 weeks. Close contact investigation if open and linked to birth parent case.	3 Days

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Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
Contact testing practitioner for Critical data elements listed on Case Form and plan for care and follow up (e.g., referral to pediatric ID for suspect or confirmed cases)	Initial contact to testing practitioner Complete PHIMS documentation • Includes classification and staging • Classification of "person under investigation" should be updated to one of the below within 4 weeks, and not remain as person under investigation after 4 weeks: ○ Lab confirmed ○ Probable (see note 1 below) ○ Suspect (see note 2 below) ○ Not a case (see note 2 below) Note: 1. Cases that meet a probable case definition should be left as probable, even if testing at 18-24 months is negative. The only exception is if they still have reactive treponemal test at ≥ 18 months old, then their classification should be changed to "lab confirmed" 2. Cases that do not meet any case definitions can be updated to "not a case" and closed. The classification can be updated if required based on subsequent laboratory results. For cases that do not meet the case definition of a lab confirmed or probable case, but public health is awaiting further information before closing the case, a classification of "case- suspect" can be used in the interim, until further information is available. This classification should be updated when further information is available, and should only be used as an interim classification unless lost to follow-up. Infants of birthing parents who were treated prior to pregnancy, had follow up serology indicating adequate treatment, and no clinical or laboratory evidence of congenital syphilis can be classified as "not a case", without health care provider confirmation.	1 Week 4 Weeks

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Investigation Component	PHIMS Data Entry	Timeline from Public Health Report Date *Days refer to working days*
Hold open for further testing if required.	Update Disposition: Hold for test results Update Classification of Probable and Suspect Cases as required as new information received.	4 weeks - 18 months
Close investigation (status): when staging and investigation complete. If unable to locate client and/or unable to meet basic care criteria (client not notified of result, no treatment provided) – hold open for at least 6 months with periodic (e.g. monthly) attempts to locate, reconnect with testing practitioner.	Disposition: Follow up Complete. Status Closed. Note: cases can be closed when staged and classified. If future test results indicate a change in classification/staging, the case can be re-opened. Disposition: Unable to Locate, OR Lost to Follow up. Status open for 6 months or more. Staging = unknown or undetermined (unable to locate or lost to follow-up is the only situation where this should be utilized, and only if there was not enough information to stage the case)	4 weeks - 18 months
Quality Assurance	All congenital syphilis cases should be reviewed within PHIMS by CD Coordinator.	6 weeks - from report date AND prior to closure

11. Additional Resources

Public Health Agency of Canada's Sexual Health and Sexually Transmitted Infections Website available at: http://www.phac-aspc.gc.ca/std-mts/index-eng.php

Public Health Agency of Canada. Canadian Guidelines on Sexually Transmitted Infections. Available at: http://www.phac-aspc.gc.ca/std-mts/sti-its/index-eng.php

Public Health Agency of Canada. Syphilis in Canada: Technical report on epidemiological trends, determinants and interventions - Canada.ca

Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease (Syphilis) Website available at: www.cdc.gov/std/syphilis/default.htm

Centers for Disease Control and Prevention (CDC) 2021 Sexually Transmitted Disease Treatment Guidelines available at:
STI Treatment Guidelines (cdc.gov)

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Sexual and Reproductive Health, World Health Organization.

https://www.who.int/health-topics/sexual-health#tab=tab_1

https://www.who.int/westernpacific/health-topics/reproductive-health

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13. Public Health Agency of Canada. Syphilis guide: treatment and follow up https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-

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