



Health, Seniors and Active Living

Public Health and Primary Health Care Division
Communicable Disease Control
4th Floor, 300 Carlton St, Winnipeg, MB R3B 3M9
T 204 788-6737 F 204 948-2190
www.manitoba.ca

June 28, 2016

Dear Health Care Provider:

Re: Benzathine Penicillin (Bicillin) Supply Shortage is Resolved

Manitoba Health, Seniors and Active Living (MHSAL) has been notified that the supply shortage of benzathine penicillin (Bicillin) has ended and that the manufacturer has sufficient supplies to meet demand in Canada.

As a result, the use of Bicillin can be resumed for the treatment of cases and contacts of Syphilis as per Manitoba's Syphilis Protocol (<http://www.gov.mb.ca/health/publichealth/cdc/protocol/syphilis.pdf>).

To order Bicillin or any other publicly-funded sexually transmitted infection (STI) treatments, the STI Medication Order Form is updated on the Government of Manitoba website and can be located at <http://www.gov.mb.ca/health/publichealth/cdc/protocol/form11.pdf>.

Reminder: All drugs that are administered as part of Manitoba's publicly-funded sexually transmitted and blood born infection program MUST be reported to MHSAL using the STI Administration Form <http://www.gov.mb.ca/health/publichealth/cdc/protocol/stiadminform.pdf>.

If you have any questions, please contact MHSAL at 204-788-6737

Sincerely,

Thank you.

"Original signed by"

Richard Baydack, PhD
Director
Communicable Disease Control

"Original signed by"

Joss Reimer, MD
Medical Officer of Health
Communicable Disease Control



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4th Floor, 300 Carlton St, Winnipeg, MB R3B 3M9
T 204 788-6737 F 204 948-2190
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June 3, 2016

Dear Health Care Provider:

Re: Update on Usage of Benzathine Penicillin (Bicillin) for the Management of Syphilis During National Shortage

Manitoba Health, Seniors and Active Living (MHSAL) is continuing to monitor the national shortage of benzathine penicillin (Bicillin), that is expected to last until at least July 2016. MHSAL has been able to acquire sufficient stock of Bicillin to expand the use of the Bicillin to provide the best possible treatment option during the current outbreak of syphilis in Manitoba.

At this time, MHSAL is recommending the following people be eligible for treatment with Bicillin:

- Pregnant individuals who are a contact of syphilis or diagnosed with primary, secondary, early latent or late latent syphilis
- All cases and contacts of infectious syphilis (primary, secondary or early latent).

Bicillin should **not** be used to treat cases of late latent syphilis. Those clients should be treated with one of the following alternative regimens (see the provincial syphilis protocol) until after the Bicillin supply chain is restored.

- Doxycycline 100mg BID X28 days (first choice), or
- Ceftriaxone 1-2g IM daily for 10-14 days for primary or secondary syphilis
- Treatment with Azithromycin is **not** recommended

Please refrain from ordering excess stock. All orders for Bicillin will be subject to review by MHSAL before being shipped.

There is no change to the recommended management for tertiary, congenital and neurosyphilis (see provincial syphilis protocol).

MHSAL will continue to update health care providers as new information is made available. In the event that the timeline of the shortage is extended or supplies become depleted further restriction on use will be implemented.

If you have any questions, please contact MHSAL at 204-788-6737

Sincerely,

Thank you.

"Original signed by"

Richard Baydack, PhD
Director
Communicable Disease Control

"Original signed by"

Joss Reimer, MD FRCPC
Medical Officer of Health
Communicable Disease Control

Public Health and Primary Health Care
Communicable Disease Control
4th Floor, 300 Carlton St, Winnipeg, MB R3B 3M9
T 204 788-6737 F 204 948-2040
www.manitoba.ca

March, 2016

Re: Syphilis Reporting and Case and Contact Investigation

Reporting of syphilis (*Treponema pallidum*) is as follows:

Laboratory:

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

Health Care Professional:

- For Public Health investigation and to meet the requirement for contact notification under the Reporting of Diseases and Conditions Regulation in the *Public Health Act*, the NEW *Syphilis Case Investigation Form* http://www.gov.mb.ca/health/publichealth/surveillance/docs/syphilis_caseinvestigation_form.pdf must be completed for all newly diagnosed cases of syphilis.
- The NEW *Contact Investigation Form for Infectious Syphilis* http://www.gov.mb.ca/health/publichealth/surveillance/docs/syphilis_contactinvestigationform.pdf must be completed for all contacts of infectious syphilis cases.
- These forms replace the *Notification of Sexually Transmitted Disease* (NSTD) form which was previously used for syphilis case and contact reporting.
- Please check with the public health office in your region with respect to procedures for return of forms for syphilis case and contact investigation.
- Cooperation with Public Health investigation is appreciated.

Regional Public Health or First Nations Inuit Health Branch:

- Return all completed investigation forms to the Public Health Surveillance Unit by mail (address on form) or secure fax (204-948-3044).

Sincerely,

“Original Signed By”

Richard Rusk, DVM, MD, CCFP, MPH
Medical Officer of Health
Communicable Disease Control

“Original Signed By”

Carla Ens, PhD
Director, Epidemiology & Surveillance
Public Health and Primary Health Care
Manitoba Health, Healthy Living and Seniors

Syphilis

1. Etiology

Syphilis is primarily a sexually transmitted bacterial infection (STI). Syphilis can also be acquired through congenital transmission to the newborn and through blood transfusion, but these are much less common. 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 developing nations and are seen in developed nations primarily as a result of immigration. Serologic testing cannot distinguish syphilis from these endemic treponematoses (3).

2. Case Definitions

2.1 Congenital Syphilis

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

Laboratory Confirmation of Infection:

Identification of *T. pallidum* by dark-field microscopy^a, fluorescent antibody^b, detection of *T. pallidum* (TP) – specific nucleic acid (using NAT, e.g., PCR – polymerase chain reaction) 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);

OR

Reactive serology (treponemal and nontreponemal with rising titres upon follow-up or titres greater than or equal to fourfold higher than those of mother when tested at the same time) from venous blood (not cord blood) in an infant/child with clinical, laboratory, or radiographic evidence consistent with congenital syphilis^c whose mother was:

- seropositive for syphilis during pregnancy or at delivery, AND
- without documented evidence of adequate treatment, OR
- demonstrated to have evidence of reinfection or relapse in pregnancy following appropriate therapy (4).

2.1.2 Late Congenital Syphilis (*greater than two years after birth*)

Laboratory Confirmation of Infection:

Reactive treponemal serology (regardless of nontreponemal test reactivity) along with characteristic late manifestations of congenital syphilis^d in a child whose mother 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).

-
- a Not available in most medical laboratories including Cadham Provincial Laboratory (CPL).
 - b Fluorescent antibody testing for syphilis is not routinely available in Manitoba but may be used in exceptional circumstances.
 - c Includes any evidence of congenital syphilis on physical examination (e.g., hepatosplenomegaly), evidence of congenital syphilis on radiographs of long bones, a reactive CSF (cerebrospinal fluid) VDRL (Venereal Disease Research laboratory test), an elevated CSF cell count or protein without other cause.
 - d An older child may have stigmata (e.g., interstitial keratitis, nerve deafness, anterior bowing of shins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, rhagades, or Clutton joints) (5).

2.2 Primary Syphilis

Laboratory Confirmation of Infection:

Identification of *T. pallidum* by dark-field microscopy^e, fluorescent antibody^f, TP-specific nucleic acid (using NAT, e.g., PCR – polymerase chain reaction), or equivalent examination of material from a chancre, consistent mucocutaneous lesion, or regional lymph node;

OR

Presence of one or more typical lesions (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 (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 treatment (4).

2.3 Secondary Syphilis

Laboratory Evidence of Infection:

Identification of *T. pallidum* by dark-field microscopy^e, fluorescent antibody^f, nucleic acid testing, 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., 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).

2.4 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.

Laboratory Confirmation of Infection:

An asymptomatic person with reactive serology (treponemal and/or nontreponemal) 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) Exposure to a sex partner with primary, secondary or early latent syphilis (4).

2.5 Late Latent Syphilis (greater than one year after infection or of unknown duration)

Laboratory Confirmation of Infection:

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).

2.6 Neurosyphilis

2.6.1 Infectious Neurosyphilis (less than one year after infection)

Laboratory Confirmation of Infection:

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

- 1) Reactive CSF-VDRL (Venereal Disease Research Laboratory test) in non-bloody cerebrospinal fluid (CSF) followed by reactive treponemal-specific antibodies on CSF;
- 2) Clinical evidence of disease consistent with neurosyphilis AND either elevated CSF leukocytes OR elevated CSF protein, in absence of other known causes (4).

Neurosyphilis may be seen during primary or secondary syphilis stages and can occur at any time after initial infection.

^e Not available in most medical laboratories including Cadham Provincial Laboratory.

^f Fluorescent antibody testing for syphilis is not routinely available in Manitoba but may be used in exceptional circumstances.

2.6.2 Non-infectious Neurosyphilis (greater than one year after infection)

Laboratory Confirmation of Infection:

Reactive treponemal serology (regardless of nontreponemal serology reactivity), AND not congenital, primary, secondary or early latent syphilis, AND one of the following:

- 1) Reactive CSF-VDRL in non-bloody CSF; or
- 2) Clinical evidence of neurosyphilis AND either elevated CSF leukocytes or elevated CSF protein in the absence of other known causes (4).

2.7 Tertiary Syphilis other than Neurosyphilis:

Laboratory Confirmation of Infection:

Reactive treponemal serology (regardless of nontreponemal test reactivity) together with characteristic late abnormalities of the cardiovascular 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); AND

No clinical or laboratory evidence of neurosyphilis (4).

3. Reporting and Other Requirements

Laboratory:

- All positive nontreponemal and treponemal test results are reportable by laboratory operators to the Manitoba Health Public Health Surveillance Unit (204-948-3044 secure fax) as indicated in Table 2: Interpretation of Serologic Tests for Syphilis.
- Operators of medical laboratories in Manitoba that detect syphilis by serology or direct examination shall forward residual positive specimens to Cadham Provincial Laboratory (CPL) within seven days of report.

Health Care Professional:

- All cases and contacts are reportable by attending health care professionals to the Manitoba Health Public Health Surveillance Unit using the

Notification of Sexually Transmitted Disease (NSTD) form available at:

<http://www.gov.mb.ca/health/publichealth/cdc/protocol/form3.pdf>.

To assist in timely public health follow-up of cases and contacts, and ensuring accuracy in surveillance reports, it is recommended that information for confirmed infectious cases be returned via the NSTD form as soon as possible to the Manitoba Health Public Health Surveillance Unit (204-948-3044 secure fax).

4. Epidemiology

4.1 Reservoir

Humans.

4.2 Transmission

Approximately 90% of all syphilis is sexually transmitted. Exposure mainly occurs during oral, anal, or 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). Early latent syphilis is considered infectious as there is a 25% chance of relapse to secondary stage (7).

Transmission following touching children with congenital syphilis, kissing, blood transfusion, sharing of needles and drug equipment, accidental direct inoculation (e.g., needlestick injury), and solid organ transplantation are extremely rare (7). Ulcerative STIs like syphilis promote HIV transmission and/or acquisition by augmenting HIV infectiousness and susceptibility. Syphilis increases the rate of HIV acquisition between two and fourfold and the risk of transmission of HIV between two and ninefold (8).

Pregnant women can transmit the infection transplacentally to the fetus at all stages during the course of untreated disease or during passage through the birth canal (9). The risk of transmission in untreated women is 70-100% with primary or secondary syphilis, 40% with early latent syphilis and 10% in late latent stages in

pregnancy (7). Breastfeeding does not result in syphilis transmission unless an infectious lesion is present on the breast (10).

4.3 Occurrence

4.3.1 Infectious Syphilis

The incidence of infectious syphilis in Canada was very low in the 1990s with most cases being imported rather than locally acquired. Rates of infectious syphilis were 0.4-0.6/100,000 in Canada from 1994 to 2000 (7), and rose to 1.5/100,000 in 2002 and 3.5/100,000 in 2004 (11). The rate of infectious syphilis reported in 2010 was 5.2 cases per 100,000 population (12). In 2010, men accounted for 90.5% of all reported infectious syphilis cases in Canada (12).

Infectious syphilis (and other bacterial STI) rates have been low in Manitoba, while many other provinces and territories have seen substantial increases in infectious syphilis over the past five to six years (12). In 2012, there were 26 confirmed cases of infectious syphilis in Manitoba, the highest reported number since 2007. Cases were predominantly male, with an age range of 19 to 57 years.

Comparatively, 1,757 cases of infectious syphilis were reported at the national-level (from across Canada) in 2010, for a national rate of 5.2 cases per 100,000 population (12). Manitoba's reported infection rate that year is well below this level (at 1.4 per 100,000 population) (12).

Localised outbreaks within Manitoba, have occurred in 2013, resulting in a notable increase in the reported number of infectious cases. This emphasizes the need for continuous vigilance in order to limit transmission of syphilis. Urban outbreaks (in the Winnipeg Health Region) that occurred in 2003 and 2005 were quickly contained, due to the extensive public health efforts of the region. The increasing use of social media and social networking sites on the internet has been a new challenge in case and contact tracing within the current outbreak situation.

4.3.2 Congenital Syphilis

The Canadian rate of congenital syphilis increased between 2000 and 2010, from less than one case per 100,000 population per year, to 2.6 cases per

100,000 in 2009 (12). In 2010, the reported rate for Canada as a whole, was 1.6 per 100,000 live births, (based on 6 reported cases) (12), while in Manitoba the rate was zero (i.e., there were no reported cases). While other provinces have seen an unexpected increase in congenital syphilis cases in recent years, Manitoba's rate of congenital syphilis has been zero (between 2000 and 2012).

4.4 Incubation Period

For a primary chancre, the incubation period is three days to three months, usually about three weeks (3). Refer to Table 1: Clinical Manifestations and Incubation Period for further details.

4.5 Period of Communicability

Variable. Syphilis is infectious during primary, secondary, and early latent stages, and also in mucocutaneous recurrences. Congenital transmission is most likely during primary and secondary maternal syphilis, but can occur in the latent period.

5. Clinical Presentation and Natural History

5.1 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).

5.2 Primary Syphilis

Primary syphilis most often presents as a single painless lesion (chancre) that develops at the site of inoculation. The chancre is most commonly found on the external genitalia. These lesions frequently go unnoticed, particularly among women and MSM (men who have sex with men), who cannot see vaginal or anal lesions. The ulcer is clean-based with a raised, indurated border. In men, the most common site affected is the penis, particularly the coronal sulcus and glans. Anorectal chancres are common in MSM.

In women, the most common locations for lesions are the labia majora, labia minora, fourchette, and perineum. Ulcers may also be found on the lip, in the mouth, and on fingers. The chancre usually resolves spontaneously in one to four months. Painless, firm regional lymphadenopathy, often associated with genital lesions, is common and occurs in up to 80% of patients. These clinical findings usually occur about three weeks after infection with *T. pallidum*.

Variations in clinical presentation have been reported in HIV infected patients. These variations include multiple single chancres and chancres that may be slower to resolve (13).

5.3 Secondary Syphilis

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. The rash of secondary syphilis is somewhat unique in that it involves the palms of the hands and soles of the feet. The rash usually resolves without scarring over several weeks. Hair loss can also occur.

Condylomata lata are characteristic of secondary syphilis. They are large fleshy lesions that may form in warm moist areas such as the perineum and perianal skin, axillae, and beneath the breasts. These lesions are painless but highly infectious.

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

Constitutional symptoms such as fevers, muscle aches, and weight loss are also common. There may be evidence of central nervous system involvement in a number of cases. Headache is present in about 30% of patients. Symptomatic meningitis may occur in up to 1-2% of cases; however, asymptomatic meningitis is more common and can occur in up to 40%.

5.4 Latent Syphilis

Left untreated, secondary syphilis may progress to a period of subclinical infection. During the latent stage of syphilis, skin lesions resolve and patients are asymptomatic. The only evidence for the diagnosis of latent infection is a positive serologic test for syphilis.

Latent syphilis is divided into early latent and late latent syphilis. Patients are classified as having early latent disease if they are asymptomatic and have acquired the infection within the past year.

Early latent syphilis can be established only in patients who have seroconverted within the past year, who have had symptoms of primary or secondary syphilis within the past year or who have had a sex partner with primary, secondary or early latent syphilis within the past year. Patients who do not meet these criteria should be presumed to have late latent syphilis or latent syphilis of unknown duration. A patient with early latent syphilis is considered to be infectious due to the 25% risk of relapse to secondary syphilis. Early latent syphilis is infectious by sexual contact whereas late latent syphilis is not. However, a pregnant woman with late latent syphilis can infect her fetus in utero, and an infection can be transmitted via transfusion of contaminated blood.

5.5 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 and cardiovascular syphilis, but not to all neurosyphilis. These forms of syphilis are now uncommon.

- **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.

- **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. The ascending aorta is most often affected, with the potential complications of valve insufficiency and coronary artery stenosis. Approximately 11% of untreated patients progress to cardiovascular syphilis.

5.6 Neurosyphilis

Central nervous system (CNS) disease can occur during any stage of syphilis. 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 (14). Asymptomatic neurosyphilis occurs in up to 40% of patients (3).

Neurosyphilis is divided into early (acute) neurosyphilis and late (chronic) neurosyphilis (3). Both early and late neurosyphilis can be divided into asymptomatic and symptomatic phases. The symptomatic phase of late neurosyphilis is further distinguished as meningovascular or parenchymatous neurosyphilis (3). Clinical overlap with combinations of meningovascular and parenchymatous features are common as this form of chronic meningitis involves every part of the CNS (3).

5.7 Syphilis in Pregnancy and Congenital Syphilis

Syphilis can be transmitted transplacentally to the fetus at all stages during the course of untreated maternal disease from incubating syphilis to primary, secondary, tertiary, and latent disease (13). Syphilis can also be transmitted during passage through the birth canal when the newborn infant contacts a genital lesion (9). 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. The rate of perinatal transmission in untreated women is 70-100% in primary syphilis, 40% for early latent syphilis, and 10% for latent disease. The longer the interval between infection and pregnancy, the more benign is the outcome in the infant.

Syphilis in pregnancy can cause widespread complications for both the infected mother and fetus. At least two-thirds of all babies born to untreated women with syphilis are infected (15). If evidence of syphilis is present, treatment should be initiated immediately according to the stage of the disease. Efficacy of syphilis treatment in pregnancy considers resolution of maternal infection and prevention of congenital syphilis.

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. Late congenital syphilis usually manifests near puberty. Most clinical signs of early congenital syphilis develop within the first three months of life. Snuffles or persistent rhinitis is one of the earliest clinical manifestations occurring in 4-22% of infants. The nasal discharge may be profuse, purulent, or blood-tinged and is highly infectious. Hepatomegaly with or without splenomegaly occurs in 33-100% of patients. Asymptomatic central nervous system involvement manifesting in CSF abnormalities of lymphocytosis, elevated protein levels, and positive serologic tests occur in up to 80% of infected infants. Symptomatic neurosyphilis develops rarely. Bone lesions develop within eight months of birth in early congenital syphilis. Late manifestations of congenital syphilis include Hutchinson's triad of interstitial keratitis, peg-shaped upper incisors, and eighth cranial nerve deafness. The hearing loss can be sudden and usually occurs at eight to 10 years of age.

5.8 HIV and Syphilis

Coinfection is common as both syphilis and HIV are sexually transmitted infections. The two infections interact in several ways. As with other ulcer-causing infections, syphilis can enhance the acquisition of HIV. Syphilis in the HIV-infected individual can be highly aggressive. Patients can progress from primary to tertiary syphilis over several years, as opposed to several decades in individuals not infected with HIV. Despite this progression, the conventional staging of syphilis is similar with HIV coinfection.

Although patients with syphilis and HIV coinfection have shown no distinctive or unique features from those without concurrent HIV infection, they are at increased risk to manifest a more protracted and malignant course. This includes 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 (3).

Coinfected patients should be managed in consultation with an infectious disease specialist or physician knowledgeable in HIV/AIDS.

Table 1: Clinical Manifestations and Incubation Period (7)

Stage	Clinical manifestations	Incubation period
Primary	Chancre, regional lymphadenopathy	3 weeks (3-90 days)
Secondary	Rash, fever, malaise, generalized lymphadenopathy, mucous lesions, condylomata lata, alopecia, meningitis, headaches, uveitis, retinitis	2-12 weeks (2 weeks-6 months)
Latent	Asymptomatic	Early: <1 year Late: ≥1 year
Tertiary		
Cardiovascular syphilis	Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis	10-30 years
Neurosyphilis	Ranges from asymptomatic to symptomatic with headaches, vertigo, personality changes, dementia, ataxia, presence of Argyll Robertson pupil	<2 years-20 years
Gumma	Tissue destruction of any organ; manifestations depend on site involved	1-46 years (most cases 15 years)
Congenital		
Early	Two-thirds may be asymptomatic. Fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anemia, hepatosplenomegaly, neurosyphilis	Onset <2 years
Late	Interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone and joint involvement, anemia, Hutchinson's teeth, neurosyphilis	Persistence >2 years after birth

6. Diagnosis of Syphilis

Diagnosis of syphilis is based on history, physical examination, and laboratory investigation. It is essential that the stage of syphilis be accurately assessed and documented in order to ensure appropriate management of cases and contacts. The interpretation of syphilis serology should be made with a health practitioner experienced in this area (7). Refer to Table 2: Interpretation of Serologic Tests for Syphilis.

A diagnosis of syphilis should be considered in anyone with signs or symptoms compatible with syphilis and also in the following individuals at higher risk of infection:

- Those who have had sexual contact with a known case of syphilis;
- Men who have sex with men (MSM);
- Sex workers;

- Those with street involvement/homeless;
- Injection drug users;
- Those with multiple sex partners;
- Those with a past history of syphilis, HIV and other STIs;
- Those originating from or having sex with an individual from a country with a high prevalence of syphilis; it should be noted that screening for syphilis (using a nontreponemal test) is routinely performed in all immigration applicants to Canada who are older than 15 years;
- Sex partners of any of the above (7).

Special Considerations in Pregnant Women and Newborn Infants

All pregnant women should be screened for syphilis and other STIs (including HIV) on their first prenatal visit, ideally in the first trimester (7). The screening test for syphilis should be repeated at 28-32 weeks and again at delivery in women at high

risk of acquiring syphilis (e.g., sex workers, those with multiple sex partners, injection drug users) (7). Consideration should be given to re-screening all pregnant women in areas experiencing heterosexual outbreaks of syphilis, regardless of the woman's risk profile (7). This is especially important in areas where congenital syphilis cases have been reported in women with no personal risk factors for syphilis (7).

Newborns should not be discharged from hospital prior to confirmation that either the mother or newborn infant has had syphilis serology undertaken during pregnancy or at the time of labour or delivery (7). All positive results require follow-up.

Infants presenting with signs or symptoms compatible with early congenital syphilis should be tested for syphilis even if the mother was seronegative at delivery, as she may have become infected very recently (7).

Any woman delivering a hydropic or stillborn infant at ≥ 20 weeks gestation should be screened for syphilis (7).

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

Dark-field microscopy and DFA/IFA testing of lesion exudates or tissues are the classic methods for diagnosing early syphilis, when an active chancre, mucous patch, or condyloma latum is present. It is also useful for testing nasal discharge in a neonate with snuffles. Dark-field microscopy as well as DFA/IFA are often not practical (it is not available in most medical labs including CPL). In addition, specimens must be appropriately collected and quickly examined within five to 20 minutes of collection.

6.2 Nucleic Acid Testing (NAT)

Cadham Provincial Laboratory (CPL) requests a Dacron swab be collected from suggestive mucocutaneous lesions (chancres, mucous patches, moistened condyloma latum or newborn nasal discharge) for nucleic acid testing (NAT) (e.g., PCR), and transported in a viral transport medium

vial preferably frozen or at 4°C. NAT is used for syphilis diagnosis as well as for subtyping. Prior arrangements with the lab are generally not required.

6.3 Serology

Serologic tests for syphilis are essential for diagnosis of individuals, for following the efficacy of therapy, and for screening purposes. They detect antibodies formed during the course of syphilitic infection. Treponemal serologic tests are necessary to establish a diagnosis of syphilis. Nontreponemal tests (RPR/VDRL) (Rapid Plasma Reagin/Venereal Disease Research Laboratory test) are no longer required for diagnosis but are needed for monitoring response to treatment. It should be emphasized that serologic test results for syphilis on rare occasions may be negative in active cases, especially in older patients, or very early in primary infections.

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". 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.

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 maternal blood may lead to a false positive test result. Such specimens will be stored but not tested. New specimens collected from both mother and infant by venipuncture are suitable to provide reliable results. Testing of maternal serum is preferred to

testing infant serum because infant serum can be nonreactive if maternal serology is low titre or if the infection was late in pregnancy. Contact CPL if further diagnostic strategies are sought. See Table 2: Interpretation of Serologic Tests for Syphilis.

6.3.1 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 Venereal Disease Research Laboratory slide test (VDRL) and the Rapid Plasma Reagin test (RPR). The RPR test is more sensitive than the VDRL. CPL uses both RPR and VDRL tests.

After adequate treatment of syphilis, nontreponemal tests (NTT) eventually become nonreactive. However, even with sufficient treatment, patients sometimes have a persistent low-level positive nontreponemal test referred to as a **serofast**. Nontreponemal test titres of persons 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 persons in the early stages of their first infection. In fact these persons may remain serofast for life.

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 nontreponemal tests are useful to determine the stage of the disease; a fourfold rise in titre may indicate recent infection, immunosuppression, 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, but serum frequently remains reactive, usually in low titre. As with all quantitative serologic tests, only a fourfold or greater change in titre is meaningful.

6.3.2 Specific Treponemal Tests

These tests measure antibodies against specific *T. pallidum* antigens and were used primarily to confirm the diagnosis of syphilis in patients with a reactive nontreponemal test, in the traditional syphilis testing algorithm. The principal specific treponemal antibody tests performed in most laboratories are the *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 *Treponema*-specific antibodies over time, sometimes faster in immunocompromised individuals. 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, drug addiction, toxoplasmosis, *H. pylori*, autoimmune disorders like lupus and rheumatoid arthritis, also 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.

With the advent of the so-called reverse algorithm for syphilis testing, automated platforms replaced manual testing with much faster turn-around time and much less labour. These new platforms use kits based on treponemal-specific antibodies (Chemiluminescent Microparticle Immunoassay [CMIA]) so the previous “confirmatory test” is done first and only specimens with positive results on the CMIA test are further tested by

nontreponemal tests (RPR/VDRL). Specimens with positive results for treponemal antibody on the CMIA test that subsequently test negative on nontreponemal tests, are confirmed using the second treponemal test (TP-PA).

6.4 Cerebrospinal Fluid Testing

In patients with suspected/confirmed syphilis, indications for cerebrospinal fluid (CSF) examination include the following:

1. Congenital syphilis;
2. Presence of neurologic or ophthalmic signs or symptoms;
3. Tertiary syphilis;

4. Previously treated patients who fail to achieve an adequate serologic response to treatment;
5. HIV patients with neurologic symptoms or signs, late latent syphilis, RPR $\geq 1:32$ dilutions, CD4 < 350 cells/ μL or treated syphilis with suboptimal decline in VDRL/RPR titre; some experts recommend CSF examination in all HIV coinfecting individuals with late latent or syphilis of unknown duration;
6. Some experts recommend CSF examination in all patients with RPR $\geq 1:32$ dilutions (7).

Note: The Rapid Plasma Reagin (RPR) test is not recommended for CSF testing.

Table 2: Interpretation of Serologic Tests for Syphilis

Number (Types of Cases)	Screening test (Treponemal-specific Ab) (CMIA)*	Nontreponemal Ab test (VDRL/RPR)	Second Treponemal-specific Ab test (TP-PA)	Final Syphilis Interpretation (Printed on CPL Report)	Notification to Public Health*
1	NR	ND	ND	Cannot exclude recent infection if specimens collected within 2-3 weeks after appearance of suspect lesions.	No report
2	R (no previous CMIA positive result)	NR	NR	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	R (with previous CMIA positive result)	NR	ND	Indeterminate. Combined with previous test results, these findings suggest a nonspecific screening test result.	No report
4	R (No previous reactive syphilis serology)	NR	R	The results suggest either recent or previous treponemal infection.	Yes
5	R (No previous reactive syphilis serology)	R	R	The results suggest either recent or previous treponemal infection.	Yes

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Number (Types of Cases)	Screening test (Treponemal- specific Ab) (CMIA)*	Nontreponemal Ab test (VDRL/RPR)	Second Treponemal- specific Ab test (TP-PA)	Final Syphilis Interpretation (Printed on CPL Report)	Notification to Public Health*
6	R (Previous reactive syphilis serology)	R	ND	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 required.	Yes
7	R (Previous reactive syphilis serology)	NR	ND	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 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, profiles 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.

Table Notes and Abbreviations:

Ab: Antibody

CMIA: Chemiluminescent Microparticle Immunoassay

RPR: Rapid Plasma Reagin test

VDRL: Venereal Disease Research Laboratory test

TP-PA: *Treponema pallidum* Particle Agglutination test – only used when screening test (CMIA) is positive but the non-treponemal test is nonreactive or there is no previous history.

NR: Nonreactive

R: Reactive

ND: Not Done

NOTES:

- The ordering practitioner will receive all results; however, public health notification is received only for the result profiles detailed in Table 2 above. Upon request, Public Health may receive other results as deemed necessary.
- Result profiles 4-7 in Table 2 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.
- To assist in timely public health follow-up of cases and contacts, and ensuring accuracy in surveillance reports, it is recommended that information for confirmed infectious cases be returned via the NSTD form as soon as possible to the Manitoba Health Public Health Surveillance Unit (204-948-3044 secure fax).
- To further assist in provincial surveillance activities it is important to provide the Manitoba Health Public Health Surveillance Unit with current case and contact information or notify them if changes occur.

6.5 Tests for Neurosyphilis

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). Consultation with an expert in the field is strongly recommended.

6.6 Tests for congenital syphilis

Venous samples should be obtained from both mother and baby for serology (treponemal and nontreponemal tests). Cord blood is not suitable for testing. The interpretation of reactive antibodies in the neonate must take into consideration the maternal history, including stage of syphilis, history of treatment, and syphilis serology results.

Placenta, neonatal nasal discharge, or skin lesions may be examined by NAT for *T. pallidum*. CSF examination should be performed on all infants with suspected congenital syphilis. Long bone x-rays should also be performed (7).

7. Key Investigations for Public Health Response

- Interview case for history of exposure, risk behaviours, sex contacts, adequacy of treatment, and promote safer sex practices. Investigation should begin within one day of public health notification, whenever possible. Cases should be prioritized based on transmission risk.
- Interview sex contacts and provide epidemiological treatment if indicated (see *Management of Sex Contacts* section), with risk assessment and promotion of safer sex practices. NOTE: All contacts are reportable to Manitoba Health under the *Public Health Act*. Please use the *Notification of Sexually Transmitted Disease* (NSTD) form available at:
<http://www.gov.mb.ca/health/publichealth/cdc/protocol/form3.pdf> to report cases and contacts.

8. Control

8.1 Management of Cases

Diagnosis of syphilis is based on history, physical examination, and laboratory investigation. It is essential that the stage of syphilis be accurately assessed and documented in order to ensure appropriate management of cases and contacts. The interpretation of syphilis serology should be made with a health care practitioner experienced in this area (7).

- Close collaboration between Public Health and Primary Care in addition to timely completion and return of NSTD forms are essential to ensure there is sufficient information to identify and locate sex 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 STIs 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, hepatitis B and human papillomavirus (HPV) if appropriate (7).
- Cases with infectious syphilis (primary, secondary, and early latent) should be interviewed for sex contacts (see *Management of Sex Contacts* section).
- Patients with confirmed infectious (primary, secondary and early latent) syphilis, and their partners, should abstain from unprotected intercourse until treatment of both partners is complete and an adequate serologic response is determined (7). Depending upon the stage of syphilis being treated, the minimum period would be three months (refer to Tables 4 and 5 for recommended follow-up testing and adequate 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:
<http://www.gov.mb.ca/health/publichealth/cdc/docs/ipc/tpap.pdf>.
- The following principles of case management apply:
 - Treat all cases of infectious syphilis immediately.
 - Interview cases within one working day whenever possible.
 - Evaluate cases within one week after treatment to document clinical response.
 - Monitor clinical and serological response (refer to Tables 4 and 5).

Manitoba Health provides drugs for treatment of bacterial STIs to practitioners in the provincial jurisdiction at no charge.

Treatment:

Refer to Table 3: Treatment of Syphilis for the specific treatment of syphilis by stage. Additional resources include the current Public Health Agency of Canada's *Canadian Guidelines on Sexually Transmitted Infections*

<http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/section-5-10-eng.php>.

- Benzathine Penicillin G (IM) is the preferred drug for treatment of all stages of adult syphilis not involving the central nervous system (7). The short-acting benzylpenicillin formulation of penicillin G is not adequate for achieving cure and should not be used (7). Practitioners and pharmacists should be aware of this to avoid inappropriate treatment. Penicillin G (IV) is preferred for neurosyphilis (7) as treponemical levels of benzathine penicillin G are not reliably achieved in the CSF (3).
- **Ordering STI Medications:** Injectable long-acting benzathine penicillin G (Bicillin-LA®) is available (**free of charge**) for the treatment of, primary, secondary, latent, and tertiary syphilis not involving the central nervous system (7). Orders can be made by completing and faxing the STI Medication Order Form available at:
<http://www.gov.mb.ca/health/publichealth/cdc/protocol/form11.pdf> as per instructions on the form. After administration of the medication, the STI Medication Administration form available at:
<http://www.gov.mb.ca/health/publichealth/cdc/protocol/stiadminform.pdf> must be completed and faxed back to Manitoba Health.
 - The product monograph will be provided with the Bicillin-LA® medication in 2 ml TUBEX sterile cartridge-needle units containing 1.2 MU of benzathine penicillin G. The dosage, administration, contraindications, and precautions sections should be reviewed thoroughly prior to use.
- Expert opinion suggests the alternative use of doxycycline for the treatment of primary, secondary and latent syphilis for non-pregnant adults who are penicillin allergic (7). However, treatment failures have been documented with the use of doxycycline. Desensitization of patients should be considered for late latent syphilis (7). This can be done orally or intravenously and in consultation with an infectious disease specialist and/or allergy specialist. Protocols for oral desensitization are found in the *Canadian Guidelines on Sexually Transmitted Infections*.
- In non-pregnant adults who are penicillin allergic, ceftriaxone can also be used as an alternative for the treatment of syphilis (7). However, penicillin desensitization should be considered for late latent and tertiary syphilis, and should be strongly considered for neurosyphilis and for pregnant patients at any stage of syphilis (7).
- Azithromycin should not be routinely used as a treatment option for early or incubating syphilis unless adequate and close follow-up can be ensured and in jurisdictions where little to no azithromycin genotypic resistance in *T. pallidum* has been demonstrated (7). This may include the epidemiologic treatment of sex contacts in the preceding 90 days to primary, secondary, and early latent syphilis cases pending the results of serologic tests where follow-up is assured (7).

- 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 disease specialist is advised if regimens other than penicillin are considered.
 - Persons for whom there is documentation of recommended treatment for syphilis being completed in the past generally need not be treated again. Retreatment should be considered when:
 - clinical signs or symptoms of syphilis persist or recur;
 - there is a fourfold increase in titre with a nontreponemal test;
 - a nontreponemal test showing a high titre initially fails to show adequate decrease following treatment (7, 14); or
 - there is a history of recent sex contact with a person with infectious syphilis (7).
 - Tables 4 and 5 provide recommendations for follow-up with nontreponemal tests and adequate serologic response respectively.
 - Persons should be retreated according to the schedules recommended for syphilis of more than one year's duration. In general, a person should be retreated only once, since they may maintain stable, low titres when nontreponemal tests are used.
- Syphilis in HIV-infected persons:**
- Persons coinfecting with HIV may require a longer course of treatment, as well as closer and longer follow-up (7). Consultation with an infectious disease specialist or physician knowledgeable in HIV/AIDS is strongly recommended.
- Syphilis in Pregnancy:**
- All women newly diagnosed with syphilis during pregnancy should receive treatment appropriate to their stage of disease (7). Refer to Table 3 for treatment recommendations and Tables 4 and 5 for nontreponemal testing and response follow-up.
 - Despite the administration of the recommended penicillin regimen, as many as 14% of women diagnosed with syphilis in late pregnancy will have fetal deaths or deliver infants with clinical evidence of congenital syphilis (7). Some experts recommend that women with primary, secondary and early latent syphilis (due to difficulty in accurately staging cases) in pregnancy receive two doses of benzathine penicillin G 2.4 MU IM one week apart (7). The effect of this regimen in preventing fetal syphilis is not known (7).
 - If there is a documented penicillin allergy, consultation with an infectious disease specialist and an allergy specialist for testing and desensitization is recommended (7).
 - Treatment of maternal syphilis can be complicated by Jarisch-Herxheimer reaction (refer to *Jarisch-Herxheimer Reaction* below), which can affect approximately 40% of pregnant women treated for syphilis and can be associated with uterine contractions and variable deceleration in fetal heart rate but usually resolves without incident (7).
 - Retreatment during pregnancy is recommended when there is:
 - clinical or serologic evidence of new infection (four-fold rise in a nontreponemal test titre);
 - serologic evidence of inadequate treatment response; or
 - history of recent sex contact with a person with infectious syphilis (7).
 - Fetal ultrasonographic abnormalities and treatment failure in pregnancies of less than 20 weeks duration are rare (7). If ultrasound is normal, the mother can be treated on an outpatient basis and be advised to seek medical attention promptly if she experiences fever, decreased fetal movement or regular contractions within 24 hours of treatment (7).
 - If the mother is greater than 20 weeks gestation, an ultrasound should be performed and she should be managed with an obstetrician/fetal-maternal medicine specialist; if fetal abnormalities

are identified (e.g., ascites, placental thickening, hepatomegaly), the mother should be hospitalized for treatment and fetal monitoring (7).

- All babies should be assessed at delivery by a pediatric specialist (e.g., Infectious Diseases) to determine if empirical treatment for congenital syphilis is indicated, especially if a maternal non-penicillin regimen was used.

Congenital Syphilis:

Infected infants are frequently asymptomatic at birth and may be seronegative if maternal infection occurred late in gestation (7). Consultation with Infectious Diseases and Pediatric Infectious Diseases is recommended for treatment and follow-up of suspected or confirmed cases of congenital syphilis.

Syphilis in Children:

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:

http://www.pacca.mb.ca/ESW/Files/Handbook_Child_Protection_and_Child_Abuse_Web_Links.pdf

Jarisch-Herxheimer Reaction:

It is a reaction to endotoxins released by the death of microorganisms within the body. It is 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).
- More common in secondary syphilis (70-90%), but can occur at any stage of infection (7).
- **Not clinically significant unless there is neurologic or ophthalmologic involvement or in pregnancy where it may cause fetal distress and premature labour (7).**
- Not a drug allergy (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).

Table 3: Treatment of Syphilis

Based on the Public Health Agency of Canada's *Canadian Guidelines on Sexually Transmitted Infections*, January 2010.

Stage	Preferred Treatment ^g	Alternative Treatment for Penicillin-allergic Patients
All non-pregnant adults <ul style="list-style-type: none"> • Primary • Secondary • Early latent <1 year duration 	Benzathine penicillin G 2.4 million units IM as a single dose ^h	<ul style="list-style-type: none"> • Doxycycline 100 mg PO bid for 14 days Alternative agents (to be used in exceptional circumstances)ⁱ <ul style="list-style-type: none"> • Ceftriaxone 1g IV or IM daily for 10 days
All non-pregnant adults <ul style="list-style-type: none"> • Late latent syphilis (>1 year duration) • Latent syphilis of unknown duration • Cardiovascular syphilis and other tertiary syphilis not involving the central nervous system 	Benzathine penicillin G 2.4 million units IM weekly for 3 doses	<ul style="list-style-type: none"> • Consider penicillin desensitization • Doxycycline 100 mg PO bid for 28 days Alternative agents (to be used in exceptional circumstances)ⁱ <ul style="list-style-type: none"> • Ceftriaxone 1 g IV or IM daily for 10 days

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Stage	Preferred Treatment ^g	Alternative Treatment for Penicillin-allergic Patients
All adults Neurosyphilis	Penicillin G 3-4 million units IV q 4 h (16-24 million units/day) for 10-14 days	<ul style="list-style-type: none"> Strongly consider penicillin desensitization followed by treatment with penicillin Ceftriaxone 2 g IV/IM qd x 10-14 days
Epidemiological treatment of sexual contacts in the preceding 90 days to primary, secondary and early latent syphilis ^j	Benzathine penicillin G 2.4 million units IM as a single dose	<ul style="list-style-type: none"> See comment below on azithromycin^k
Pregnant women <ul style="list-style-type: none"> Primary Secondary Early latent (<1 year duration) 	Benzathine penicillin G 2.4 million units IM weekly for 1-2 doses ^{h, l}	<ul style="list-style-type: none"> 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.
Pregnant women <ul style="list-style-type: none"> Late latent syphilis Latent syphilis of unknown duration Cardiovascular syphilis and other tertiary syphilis not involving the central nervous system 	Benzathine penicillin G 2.4 million units IM weekly for 3 doses	<ul style="list-style-type: none"> 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.

g Reports from some jurisdictions have indicated inappropriate use of short-acting benzylpenicillin (penicillin G) (IM) for the treatment of infectious syphilis rather than long-acting benzathine penicillin G (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 2-4 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 3 weekly doses (total of 7.2 million units) of benzathine penicillin G in HIV-infected individuals (7).

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

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

k **Azithromycin:** In light of recent reports of failure of azithromycin for the treatment of early syphilis and the rapid development of azithromycin resistance in *T. pallidum*, this agent should not be routinely used as a treatment option for early or incubating syphilis, unless adequate and close follow-up can be ensured, and only in jurisdictions where little or no azithromycin genotype resistance in *T. pallidum* has been demonstrated. It should be noted, however, that at the present time, very limited Canadian data on the prevalence of azithromycin resistance in *T. pallidum* is available.

l Given the complexity of accurately staging early syphilis, some experts recommend that primary, secondary and early latent cases in pregnancy be treated with two doses of benzathine penicillin G 2.4 million units one week apart; the efficacy of this regimen in preventing fetal syphilis is not known.

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 4 for recommended 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 5: Adequate Serologic Response.

Table 4: Recommended Nontreponemal Testing (NTT) Following Treatment (7)

Primary, secondary, early latent	(*), 3, 6, 12 months after treatment ⁺
Late latent, tertiary (except neurosyphilis)	12 and 24 months after treatment [#]
Neurosyphilis	6, 12 and 24 months after treatment. Patients with CSF abnormalities require follow-up CSF at 6 month intervals until normalization of CSF parameters (7).
HIV-infected (any stage)	(*), 3, 6, 12, 24 months after treatment and yearly thereafter.
Congenital syphilis	Consultation with Infectious Diseases and Pediatric Infectious Diseases is recommended.

* Some experts recommend follow-up testing at one month after treatment to ensure that nontreponemal test titre is not rising: a rising titre may be indicative of either treatment failure or reinfection (7).

+ In pregnant women at high risk of reinfection (refer to Diagnosis section for risk factors), serologic testing should be increased to monthly until delivery (7).

In pregnant women, also test at time of delivery (7).

Table 5: 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 and 16-fold drop at 6 and 12 months respectively
Early latent syphilis	4-fold drop at 12 months

* A four-fold drop = 2 – tube drop (e.g., change from 1:32 dilutions to 1:8 dilutions)

NOTES:

- NTT may revert to nonreactive after treatment or remain at a low steady level (e.g., $\leq 1:4$ 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 coinfecting with HIV (7).

8.2 Management of Sex Contacts (Partner Notification) and Perinatal Contacts

- Rapid identification and investigation of sex partners/contacts is essential to locate persons with early (primary, secondary, early latent) or incubating syphilis and provide them with treatment to prevent further transmission. Regulations under the *Public Health Act* require health care professionals to report all sex contacts to Manitoba Health. Please use the *Notification of Sexually Transmitted Disease* (NSTD) form available at:
<http://www.gov.mb.ca/health/publichealth/cdc/protocol/form3.pdf> to report cases and contacts.
- Primary, secondary and early latent stages are considered infectious, with an estimated risk of transmission per partner of 60% (7).
- The risk of transmission to the fetus in untreated women is 70-100% with primary or secondary syphilis, 40% with early latent syphilis and 10% in late latent stages in pregnancy (7). Breastfeeding does not result in syphilis transmission unless an infectious lesion is present on the breast (10).
- All sex 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:
 - To include additional time up to the date of treatment;
 - If the index case states that there were no sex partners during the recommended trace-back period, then the last partner should be notified.
 - If all partners traced (according to recommended trace-back period) test negative, then the partner prior to the trace-back period should be notified (7).

Presumptive or epidemiologic treatment of sex partners should be considered under the following circumstances (refer to Table 3 for treatment recommendations):

- Persons who were exposed within three months preceding the diagnosis of primary, secondary or early latent syphilis in a sex partner 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 sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.

Patient's Stage of Syphilis	Trace-back Period*
Primary syphilis	3 months
Secondary syphilis	6 months
Early latent	One year
Late latent/tertiary	Assess marital or other long-term partners and children as appropriate; the decision to test these contacts depends on estimated duration of infection in source case.
Congenital	Assess mother and her sex partner(s).
Stage undetermined	Assess/consult with a colleague experienced in syphilis management and/or with a Medical Officer of Health.

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

8.3 Preventive Measures

- Education for sexually active patients on the transmission risks associated with various sex acts (e.g., oral, vaginal, anal) (7).
- Education on risk reduction behaviours (e.g., sexual abstinence, reducing the number of sex partners, proper and consistent use of barrier methods) (7).
- Routine prenatal screening and screening of individuals at higher risk of infection. Refer to Section 6. *Diagnosis of Syphilis*.
- Case and contact management as per this protocol.
- 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 reported to Manitoba Health.

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:
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