

Syphilis

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SYPHILIS

Etiology

- Caused by *Treponema pallidum* subsp. *pallidum*.
- *T. pallidum* subsp. *pallidum* causes venereal syphilis, *T. pallidum* subsp. *endemicum* causes endemic syphilis (bejel), *T. pallidum* subsp. *pertenue* causes yaws and *T. carateum* causes pinta.

Epidemiology

- Infectious syphilis (primary, secondary and early latent stages) is the least common of the three nationally reportable bacterial sexually transmitted infections (STIs).¹
- After achieving rates of 0.4–0.6/100,000 from 1994 to 2000, rates of infectious syphilis started to rise. The projected figures for 2008 show a reported rate of 4.0/100,000.^{1,2}
- The rate of infectious syphilis is increasing in both males and females, but more so in males. In recent years, localized outbreaks of infectious syphilis have been reported in a number of locations worldwide^{3, 4} and in Canada, including Vancouver, Yukon, Calgary, Edmonton, Northwest Territories, Winnipeg, Toronto, Ottawa, Montreal and Halifax.^{2, 5–7}
 - Most of the outbreaks have been in men who have sex with men (MSM) and other outbreaks related to sex trade but some have been locally acquired infections in heterosexual persons not fitting into one of these categories. Some large outbreaks among MSM primarily in the United States have been associated with the acquisition of anonymous sex partners through the Internet.⁸ Similar findings have been reported from Calgary, Alberta.⁹
- Based on data from British Columbia (B.C.), Alberta and Yukon, Aboriginal people in these two provinces and one territory are disproportionately affected by STIs.
- Nationally, 2 congenital cases or less a year were reported in the decade before 2005. No cases of congenital syphilis were reported in Canada in 2003 and 2004.¹⁰ In 2005 there were 8 cases (5 from Alberta, 3 from B.C.), in 2006 there were 7 cases (4 from Alberta, 2 from B.C. and 1 from Ontario) and in 2007, there were 8 reported cases (5 from Alberta, 2 from B.C. and 1 from Ontario). Preliminary data show another 7 cases with similar geographic distribution were reported in 2008, highlighting the continuation of this worrisome trend.⁷
- **Syphilis, as with other STIs, increases the risk of acquisition and transmission of HIV.**

Transmission

- The primary mode of transmission is by vaginal, anal and oral sexual contact.¹¹
- Kissing (oral oral contact), sharing of needles and injection equipment, blood transfusion, accidental inoculation (e.g., needle stick injury) and solid organ transplantation have rarely been reported as routes of transmission.^{12,13}
- Primary, secondary and early latent stages are considered infectious, with an estimated risk of transmission per partner of around 60%.¹⁴ Direct (often intimate) contact with lesions of primary and secondary syphilis poses the greatest risk of transmission. Early latent syphilis is considered infectious because of the 25% chance of relapse to secondary stage.¹⁵
- The majority of infants with congenital syphilis are infected in utero, but they can also be infected by contact with an active genital lesion at the time of delivery. 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.^{16,17} About 40% of pregnancies in women with infectious syphilis results in fetal demise.¹⁸
- Breastfeeding by mothers with primary or secondary lesions of syphilis carries a theoretical risk of transmission of syphilis to the baby.

Prevention and Control

- Sexual activity of any mucosal type - oral, anal or genital – can be a mode of transmission for syphilis. Although direct (often intimate) contact with lesions of primary and secondary syphilis poses the greatest risk of transmission, the lesions may not be readily apparent (e.g., painless lesions on the internal genital tract in females, intra-anal lesions, etc.) and as such all patients with infectious syphilis should be considered potentially infectious regardless of the presence or absence of obvious lesions. It is important that health professionals accurately communicate the risks associated with various sex acts to sexually active patients, including the risk of transmission via oral sex and ensure the use of a barrier method for oral sex (i.e., although the risk of STI transmission is lower via oral sex than vaginal or anal sex, many STIs, including syphilis can be transmitted through unprotected oral sex).
- Asymptomatic patients presenting with concerns about STIs and/or birth control should be given information on the efficacy of barrier methods in preventing STI/HIV transmission and provided safer sex counselling (see *Primary Care and Sexually Transmitted Infections* chapter).
- Persons presenting with concerns about syphilis (or STI/HIV) provide an important opportunity for education and encouragement for consistent practice of risk reduction behaviours. These practices include, but are not limited to, sexual abstinence, reducing the number of sexual partners and proper and consistent use of barrier methods (see *Primary Care and Sexually Transmitted Infections* chapter).
- Identify barriers to prevention practices and the means to overcome them (see *Primary Care and Sexually Transmitted Infections* chapter).
- In patients with confirmed infectious (primary, secondary and early latent) syphilis, patients and their partners should abstain from unprotected intercourse until treatment of both partners is complete and an adequate serologic response is determined (see *Follow-up* section, below).
- Syphilis can also be passed from mother to child during pregnancy and therefore routine prenatal screening for syphilis is an important means of prevention (see *Diagnosis* section under *Special considerations in pregnant women and newborn infants* in the current chapter).

- In cases where a child is born to a mother who was diagnosed with syphilis in pregnancy, and where the child is placed under the care of child protection services, medical information about the mother's diagnosis may be critical to the ongoing protection and monitoring of the infant's health. It is important to facilitate the collection and disclosure of relevant health information, in accordance with provincial/territorial requirements, in order to allow appropriate follow-up care (see *Special considerations* section in the current chapter under *Pregnancy*).
- *Cycling of syphilis epidemics*: Data presented in 2005¹⁹ proposed, based on analysis of a U. S. Centers for Disease Control and Prevention (CDC) dataset, that syphilis epidemics cycle and that these cyclic dynamics are a result of innate immunity rather than treatment or behavioural changes. However, more recent data from Breban et al²⁰ found that in contrast to the previous model, their analysis did not support the cycling of syphilis epidemics. These authors concluded that prevention and control measures initiated by the CDC could be successful in eliminating syphilis in the United States within the next few decades.

Manifestations

Table 1. Manifestations¹¹

Stage	Clinical manifestations	Incubation period
<i>Primary</i>	Chancre, regional lymphadenopathy	3 weeks (3–90 days)
<i>Secondary</i>	Rash, fever, malaise, lymphadenopathy, mucus lesions, condyloma lata, patchy or diffuse alopecia, meningitis, headaches, uveitis, retinitis	2–12 weeks (2 weeks–6 months)
<i>Latent</i>	Asymptomatic	Early: <1 year Late: ≥1 year
<i>Tertiary</i>		
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)
<i>Congenital</i>		
Early	2/3 may be asymptomatic Fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anemia, hepatosplenomegaly, neurosyphilis	Onset <2 years
Late	Interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone involvement, anemia, Hutchinson's teeth, neurosyphilis	Persistence >2 years after birth

Diagnosis

Risk factors

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

- Those who have had sexual contact with a known case of syphilis.
- MSM.
- Sex workers.
- Those with street involvement/homeless.
- Injection drug users.
- Those with multiple sexual partners.
- Those with a 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 non-treponemal test) is routinely performed in all immigration applicants to Canada who are older than 15 years.
- Sexual partners of any of the above.

Individuals of aboriginal ethnicity are disproportionately affected by syphilis in some geographic areas of Canada, particularly in some areas experiencing outbreaks of infectious syphilis; the decision to screen or re-screen Aboriginal persons for syphilis should be made in the context of local epidemiology.

Symptoms and signs

- Current or past history of lesions or rash (see *Manifestations*, above).
- A high proportion of individuals fail to recall a primary chancre.¹¹
- Symptoms and signs may be modified in the presence of HIV co-infection.²¹

Special considerations in pregnant women and newborn infants

- **Given the resurgence of syphilis in Canada, universal screening of all pregnant women continues to be important and remains the standard of care in most jurisdictions.**
- Initial screening should ideally be performed in the first trimester. The screening test should be repeated at 28-32 weeks and again at delivery in women at high risk of acquiring syphilis. More frequent re-screening may be indicated in some instances (see *Risk Factors*, above). Consideration should be given to re-screening all pregnant women in areas experiencing heterosexual outbreaks of syphilis, regardless of the woman's risk profile. This is especially important in areas where congenital syphilis cases have been reported in women with no personal risk factors for syphilis.
- Screening in the first trimester and at 28-32 weeks seeks to prevent the transmission of syphilis to the fetus while screening near term/delivery serves primarily to detect cases.
- Any woman delivering a hydropic or stillborn infant at ≥ 20 weeks gestation should be screened for syphilis.
- No newborn should 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 and that the results will be followed up.

- Infants presenting with symptoms or signs 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.

Laboratory diagnosis

- **The interpretation of syphilis serology should be made in conjunction with a colleague experienced in this area (see Table 2).**
- Every attempt should be made to obtain and document prior history of treatment for syphilis and prior serologic results in order to avoid unnecessary retreatment.

Tests from lesions of primary and secondary syphilis

- Dark-field microscopy, Direct/Indirect Fluorescent Antibody (DFA/IFA) or Nucleic Acid Amplification Tests (NAAT, e.g., Polymerase Chain Reaction [PCR]) are options for testing lesions of primary and secondary syphilis. For more information on available tests, please contact your local laboratory.
- Dark-field microscopy testing is used to visualize *T. pallidum* from chancres of primary syphilis and some lesions of secondary syphilis (e.g., condyloma lata).
- Dark-field microscopy and Direct/Indirect Fluorescent Antibody tests (DFA/IFA) are not reliable for oral/rectal lesions, as there may be cross-reaction with non-pathogenic treponemes in oral and anal specimens. NAAT (e.g., PCR) testing may be an option for such specimens. If NAAT testing is not available and initial serological testing is negative, repeat serology in 2-4 weeks.
- PCR is available in some jurisdictions; check with your local laboratory regarding the availability of this test.

Serology

- Screening for syphilis has traditionally involved the use of non-treponemal tests (NTT) such as rapid plasma reagin (RPR), followed by confirmatory treponemal tests if the NTT is reactive. However, in patients with suspected primary syphilis or late latent syphilis, the NTT may be non-reactive, and it is then appropriate to add a treponemal test to the initial screen or, in the case of primary syphilis, to repeat the NTT after 2–4 weeks. In regions experiencing outbreaks of syphilis and where NTT is the screening test, it may be appropriate to screen at baseline with both non-treponemal and treponemal tests.
- The introduction of treponemal enzyme immunoassays (EIA) may provide a more sensitive screening test for syphilis and are now commercially available for use in some laboratories in Canada. Although EIA is highly sensitive, the test can lack specificity and in some jurisdictions may be followed by a confirmatory test (usually another treponemal-specific test). Syphilis testing algorithms vary across Canada and it is therefore recommended that you check with your laboratory regarding local testing protocols. A NTT is still required to help stage the infection (see bullets below).
- Non-treponemal tests include RPR and venereal disease research laboratory (VDRL).
- Non-treponemal antibody titres usually correlate with disease activity and are used to help stage infection, to monitor response to treatment and to assess for reinfection.

- Treponemal tests include the *T. pallidum* particle agglutination (TP-PA), microhemagglutination-*T. pallidum* (MHA-TP), fluorescent treponemal antibody absorbed (FTA-ABS), EIA to detect IgG and/or IgM antibodies and the syphilis INNO-LIA™, a recently developed line immunoassay.
- Treponemal tests, once reactive, usually remain reactive for life regardless of treatment, although 15–25% will serorevert if the patient is treated during the primary stage.¹¹

Table 2. Guide to interpretation of serologic tests for syphilis

Test results on blood or serum			Most likely condition
INITIAL SCREEN Non-treponemal test: RPR	CONFIRMATORY ASSAY Treponemal test: TP-PA	CONFIRMATORY ASSAY Treponemal test: FTA-ABS	
Non-Reactive	Non-Reactive	Reactive	Primary syphilis with compatible history/clinical findings
Reactive (dilutions can vary)	Reactive	Reactive	Syphilis, any stage (Note that more likely to be infectious if RPR titre \geq 32 dilutions) OR Previously treated syphilis OR Follow-up of treated syphilis OR In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel OR Lyme Disease
Non-Reactive	Reactive	Reactive	Usually treated syphilis OR Early infection (early primary syphilis) OR Late latent/tertiary syphilis OR In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel OR Lyme Disease
Reactive	Non-Reactive	Non-Reactive	False positive [†]

FTA-ABS = fluorescent treponemal antibody absorbed

RPR = rapid plasma reagin

TP-PA = *T. pallidum* particle agglutination

[†] Some causes of false positive serologic tests for syphilis include certain conditions such as collagen-vascular diseases, pregnancy, injection drug use, Lyme Disease, etc or false positive reactions inherent to the kit or testing technique.

Table 2. Guide to interpretation of serologic tests for syphilis (continued)

Test results on blood or serum			Most likely condition/ recommended action
INITIAL SCREEN Treponemal test: EIA	Non-treponemal test: RPR result and titre	CONFIRMATORY TEST (if performed) [◇] Treponemal test: TP-PA, FTA-ABS or INNO-LIA™	
Negative	Not done	Not done	Not a case Repeat serology [‡] if at risk for syphilis
Borderline/ indeterminate	Non-Reactive	Negative or indeterminate	Repeat serology [‡] may be early seroconversion. <i>If repeat serology remains unchanged this is not a case of syphilis.</i>
Borderline/ indeterminate	Non-Reactive	Reactive/positive	Early primary syphilis OR Late latent/tertiary syphilis OR Previously treated syphilis OR In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel OR Lyme Disease <i>If laboratory does not perform confirmatory, then repeat serology[‡] as may be early seroconversion. In this instance, if repeat serology remains unchanged this is not a case of syphilis.</i>

EIA = enzyme immunoassay

FTA-ABS = fluorescent treponemal antibody absorbed

INNO-LIA™ = line immunoassay

RPR = rapid plasma reagin

TP-PA = *T. pallidum* particle agglutination

[‡] Serology typically repeated 2-4 weeks after initial test to observe for rise in RPR titre or to detect EIA/confirmatory test conversion.

[◇] Confirmatory tests are not done in all jurisdictions. Syphilis testing algorithms vary across Canada and it is therefore recommended that you check with your laboratory regarding local testing protocols.

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Test results on blood or serum			Most likely condition/ recommended action
INITIAL SCREEN Treponemal test: EIA	Non-treponemal test: RPR result and titre	CONFIRMATORY TEST (if performed) [◇] Treponemal test: TP-PA, FTA-ABS or INNO-LIA™	
Positive	Reactive <i>(dilutions can vary)</i> OR Non-Reactive	Negative	False positive [†] <i>If laboratory does not perform confirmatory testing, then interpretation is:</i> <i>Early primary syphilis</i> OR <i>Late latent/tertiary syphilis</i> OR <i>Previously treated syphilis</i> OR <i>In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel</i> OR <i>Lyme Disease</i>

EIA = enzyme immunoassay

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Positive	Reactive <i>(dilutions can vary)</i>	Indeterminate	Repeat serology [‡] to help determine if: Early primary syphilis OR Late latent/tertiary syphilis OR Previously treated syphilis OR In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel OR Lyme Disease If repeat serology is unchanged this is likely to be a false positive [†] <i>If laboratory does not perform confirmatory testing, interpretation is as follows:</i> <i>Syphilis, any stage</i> <i>(Note that more likely to be infectious if RPR titre ≥ 32 dilutions)</i> OR <i>Previously treated syphilis</i> OR <i>Follow-up of treated syphilis</i> OR <i>In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel</i> OR <i>Lyme Disease</i>

EIA = enzyme immunoassay; FTA-ABS = fluorescent treponemal antibody absorbed

INNO-LIA™ = line immunoassay; RPR = rapid plasma reagin; TP-PA = *T. pallidum* particle agglutination

[†] Some causes of false positive serologic tests for syphilis include certain conditions such as collagen-vascular diseases, pregnancy, injection drug use, Lyme Disease, etc or false positive reactions inherent to the kit or testing technique.

[‡] Serology typically repeated 2-4 weeks after initial test to observe for rise in RPR titre or to detect EIA/confirmatory test conversion.

[◇] Confirmatory tests are not done in all jurisdictions. Syphilis testing algorithms vary across Canada and it is therefore recommended that you check with your laboratory regarding local testing protocols.

Table 2. Guide to interpretation of serologic tests for syphilis (continued)

Test results on blood or serum			Most likely condition/ recommended action
INITIAL SCREEN Treponemal test: EIA	Non-treponemal test: RPR result and titre	CONFIRMATORY TEST (if performed) [◇] Treponemal test: TP-PA, FTA-ABS or INNO-LIA™	
Positive	Non-Reactive	Indeterminate	Repeat serology [‡] to help determine if: Early primary syphilis OR Late latent/tertiary syphilis OR Previously treated syphilis OR In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel OR Lyme Disease If repeat serology is unchanged this is likely to be a false positive [†] <i>If laboratory does not perform confirmatory testing, interpretation is as follows:</i> <i>Early primary syphilis</i> OR <i>Late latent/tertiary syphilis</i> OR <i>Previously treated syphilis</i> OR <i>In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel</i> OR <i>Lyme Disease</i>

EIA = enzyme immunoassay; FTA-ABS = fluorescent treponemal antibody absorbed

INNO-LIA™ = line immunoassay; RPR = rapid plasma reagin; TP-PA = *T. pallidum* particle agglutination

[†] Some causes of false positive serologic tests for syphilis include certain conditions such as collagen-vascular diseases, pregnancy, injection drug use, Lyme Disease, etc or false positive reactions inherent to the kit or testing technique.

[‡] Serology typically repeated 2-4 weeks after initial test to observe for rise in RPR titre or to detect EIA/confirmatory test conversion.

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Table 2. Guide to interpretation of serologic tests for syphilis (continued)

Test results on blood or serum			Most likely condition/ recommended action
INITIAL SCREEN Treponemal test: EIA	Non-treponemal test: RPR result and titre	CONFIRMATORY TEST (if performed) [◇] Treponemal test: TP-PA, FTA-ABS or INNO-LIA™	
Positive	Non-Reactive	Reactive/Positive	Early primary syphilis OR Late latent/tertiary syphilis OR Previously treated syphilis OR In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel OR Lyme Disease
Positive	Reactive (dilutions can vary)	Reactive/Positive	Syphilis, any stage (Note that more likely to be infectious if RPR titre ≥ 32 dilutions) OR Previously treated syphilis OR Follow-up of treated syphilis OR In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel OR Lyme Disease

EIA = enzyme immunoassay

FTA-ABS = fluorescent treponemal antibody absorbed

INNO-LIA™ = line immunoassay; RPR = rapid plasma reagin; TP-PA = *T. pallidum* particle agglutination

[◇] Confirmatory tests are not done in all jurisdictions. Syphilis testing algorithms vary across Canada and it is therefore recommended that you check with your laboratory regarding local testing protocols.

Cerebrospinal fluid

- In patients with suspected/confirmed syphilis, criteria for cerebrospinal fluid (CSF) examination include the following:
 - Presence of neurologic or ophthalmic symptoms or signs.
 - Congenital syphilis.
 - Previously treated patients who fail to achieve an adequate serologic response to treatment.
 - Tertiary syphilis.²²
 - HIV patients with neurologic symptoms or signs²³, 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-infected individuals.²⁴
 - Some experts recommend CSF examination in all patients with RPR $\geq 1:32$ dilutions.²⁴
- CSF should be tested for cell count and differential, protein, VDRL and/or FTA-ABS.
- CSF-VDRL is highly specific but insensitive.
- CSF FTA-ABS is highly sensitive but non-specific for neurosyphilis; a negative CSF FTA-ABS helps to exclude a diagnosis of neurosyphilis.^{22,25-27}
- 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.

Management

Primary and secondary syphilis

- Attempt to obtain material from primary or secondary lesions for dark-field microscopy and/or DFA/IFA for *T. pallidum* except for oral and anal lesions. The DFA/IFA for *T. pallidum* may cross-react with non-pathogenic treponemes in oral and anal specimens.
- **Serologic testing should always be performed** but it should be noted that both non-treponemal and treponemal tests may be negative in early primary syphilis. Serology should be repeated in 2–4 weeks if suspect primary lesions are dark-field or DFA/IFA negative and/or no treatment has been given. If follow-up cannot be assured, it may be appropriate to treat presumptively for primary syphilis.
- Ulcers should always be tested for herpes simplex virus and/or chancroid (if epidemiologically appropriate; see *Chancroid* chapter) and/or lymphogranuloma venereum (if epidemiologically appropriate; see *Lymphogranuloma venereum* chapter).

Latent syphilis

- Serologic testing should always be performed but it should be noted that a non-reactive non-treponemal test may be seen in latent syphilis.
- All patients should undergo a physical examination, including neurologic examination, to evaluate for the presence of signs of tertiary syphilis. Chest X-ray may be appropriate to evaluate for the presence of cardiovascular syphilis (e.g., aneurysm of ascending aorta).
- Lumbar puncture may be appropriate in select circumstances (see *Cerebrospinal Fluid*, above).
- Treat as appropriate for stage.

Tertiary syphilis

- Serology: both treponemal and non-treponemal tests to establish the diagnosis; note that a negative non-treponemal test does not rule out the diagnosis of tertiary syphilis.
- All patients with suspected tertiary syphilis should undergo CSF examination.
 - If CSF is not compatible with a central nervous system (CNS) infection, treat as for late latent syphilis.
 - If unable to obtain CSF examination or if CSF is compatible with a CNS infection, treat as for neurosyphilis.

Congenital syphilis (see Table 8b)²⁸

- Obtain venous samples from both mother and baby (note that cord blood is not suitable) for serology (treponemal and non-treponemal tests).
 - 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 dark-field microscopy or DFA/IFA or PCR for *T. pallidum*. It is unknown if the DFA/IFA cross-reacts with non-pathogenic treponemes from these specimen types.
- CSF examination should be performed on all infants with suspected congenital syphilis.
- Long-bone X-rays should be performed.

Treatment

- Although regimens containing daily IM procaine penicillin for 10–14 days are equally efficacious to regimens containing benzathine penicillin G, the latter are preferred because of better adherence with less frequent dosing (weekly).
- Benzathine penicillin G is commercially available in Canada and it is no longer necessary to access it through Health Canada's Special Access Program.



Reports from some jurisdictions have indicated inappropriate use of short-acting benzylpenicillin (penicillin G) (IM) for the treatment of infectious syphilis rather than the standard 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.²⁹

Table 3. Treatment

Stage	Preferred treatment ^ψ	Alternative treatment for penicillin-allergic patients
All non-pregnant adults • Primary • Secondary • Early latent (<1 year duration)	Benzathine penicillin G 2.4 million units IM as a single dose ^{*30-33} [A-II for NON-HIV; A-III for HIV - infected individuals]	• Doxycycline 100 mg PO bid for 14 days ³⁴⁻³⁷ [B-II] Alternative agents (to be used in exceptional circumstances) [†] • Ceftriaxone 1 g IV or IM daily for 10 days ³⁸ [B-II]
All non-pregnant adults • 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 ^{39,40} [A-II]	• Consider penicillin desensitization • Doxycycline 100 mg PO bid for 28 days ³⁵ [B-II] Alternative agents (to be used in exceptional circumstances) [†] • Ceftriaxone 1 g IV or IM daily for 10 days ⁴¹ [C-III]
All adults Neurosyphilis	Penicillin G 3–4 million units IV q 4 h (16–24 million units/day) for 10–14 days ⁴⁰ [A-II]	• Strongly consider penicillin desensitization followed by treatment with penicillin • Ceftriaxone 2 g IV/IM qd x 10–14 days ^{40,42-45} [B-II]
Epidemiological treatment of sexual contacts in the preceding 90 days to primary, secondary and early latent syphilis ^{§‡46}	Benzathine penicillin G 2.4 million units IM as a single dose [B-II]	• See comment below on azithromycin [‡]

^ψ 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.²⁹

* Some experts recommend 3 weekly doses (total of 7.2 million units) of benzathine penicillin G in HIV-infected individuals.

[†] 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.

[§] If sexual contact is unreliable or unable to test, then epidemiological treatment should be strongly considered.

[‡] **Azithromycin:** In light of recent reports of failure of azithromycin for the treatment of early syphilis⁴⁷ and the rapid development of azithromycin resistance in *T. pallidum*^{48,49}, 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 to no azithromycin genotypic 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, with 1 of 47 specimens between 2000-2003 as compared with 4 of 9 specimens from MSM in 2004-2005 collected in Vancouver demonstrating resistance.⁴⁹ A recent analysis of specimens from Alberta showed that 4 of 14 syphilis cases between February 2007 and January 2008 were azithromycin resistant; all cases were in MSM except for one neonate with congenital syphilis whose father acquired syphilis outside of Canada.⁵⁰

Table 3. Treatment (continued)

Stage	Preferred treatment [‡]	Alternative treatment for penicillin-allergic patients
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 ^{‡*51} [B-II (single dose); C-III (2 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 [A-III]
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 ⁵² [A-II]	<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 [A-III]

[‡] 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.²⁹

* Some experts recommend 3 weekly doses (total of 7.2 million units) of benzathine penicillin G in HIV-infected individuals.

[‡] 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 1 week apart; the efficacy of this regimen in preventing fetal syphilis is not known.⁵³

Table 3. Treatment (continued)

Stage	Preferred treatment ^ψ	Alternative treatment for penicillin-allergic patients
<p>Congenital syphilis⁵⁴</p> <p>(see Table 8b for recommendations from Canadian Paediatric Society)</p>	<p><1 month of age</p> <p>Crystalline penicillin G 50,000 units/kg IV every 12 hours for the first week of life and every 8 hours thereafter for 10 days of total therapy [A-II]</p> <p>Addendum:</p> <p>Benzathine penicillin G 50,000 units/kg IM in a single dose (C-III) has been recommended by some experts for infants not diagnosed with congenital syphilis but born to mothers with infectious syphilis:</p> <ol style="list-style-type: none"> 1. In whom adequate maternal treatment is confirmed <p>AND</p> <ol style="list-style-type: none"> 2. Where there is no concern regarding re-infection in the mother <p>AND</p> <ol style="list-style-type: none"> 3. In infants with with no clinical or laboratory evidence of congenital syphilis <p>Alternatively, meticulous follow up (e.g., monthly clinical/laboratory follow up) until clearance of passively transferred antibodies may be indicated if there is good indication that adequate maternal treatment occurred.</p>	
	<p>≥1 month of age</p> <p>Crystalline penicillin G 50,000 units/kg IV every 6 hours for 10–14 days [A-II]</p>	<ul style="list-style-type: none"> • If no neurologic involvement and normal CSF: benzathine penicillin G 50,000 units/kg IM (max 2.4 million units) weekly for 3 successive weeks [B-II] • No data are available to recommend penicillin alternatives in the case of penicillin allergy

^ψ 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.²⁹

Penicillin desensitization⁵⁵

- Skin testing with the major and minor determinants can reliably identify persons at high risk for penicillin reactions. Patients who have a positive skin test to one of the penicillin determinants can be desensitized. However, commercial lack of availability of the determinants used for skin testing may preclude such testing and it is advisable to proceed to desensitization and treatment in patients with a history of reaction to penicillin that is likely IgE mediated (e.g., anaphylaxis).
- Desensitizations should not be carried out for severe immunologic reactions caused by penicillins like: toxic epidermal necrolysis, Steven-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), serum sickness, acute generalized exanthematous pustulosis or agranulocytosis.
- Oral desensitization is preferable to IV desensitization, as it is safer and less costly. Informed consent should be obtained. Because penicillin desensitization has proven to be relatively safe, it is reasonable to perform the procedure in a general ward or outpatient setting, with regular monitoring and trained personnel available to respond immediately to anaphylaxis. Medications and resuscitation equipment necessary for treatment of anaphylaxis should be readily available. The whole procedure usually can be completed in 4 hours, after which the first dose of penicillin is given. After administration of the dose, the patient should be observed for at least 1 hour.
- At the completion of oral desensitization, the therapeutic dose of penicillin may be administered via the desired route. To maintain the desensitized state, the patient requires continual penicillin levels. If penicillin (short-acting) is discontinued for more than 48 hours, the patient is again at risk for anaphylaxis and desensitization should be repeated. When long acting penicillins (e.g., Bicillin-LA) are administered after desensitization, repeat doses may be safely administered at weekly intervals if required (Solensky R and Singh AE, personal communication, 2009).

Table 4. Oral desensitization protocol for patients with a positive skin test⁵⁶

Penicillin V suspension dose number*	Amount [†] units/mL	Volume administered (mL)	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

* Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose, 1.3 million units.

† The specific amount of drug is diluted in approximately 30 mL of water and then administered orally.

Consideration for other STIs

- All patients with reactive syphilis serology should be tested for HIV, as this affects treatment and follow-up.
- Testing for other STIs, including chlamydia and gonorrhea, should be performed.
- Genital ulcers should also be tested for herpes simplex virus and/or chancroid and/or lymphogranuloma venereum, depending on epidemiologic risk.
- Immunization against hepatitis B is indicated if not already immune. Immunization against hepatitis A may be indicated if not already immune. Discuss HPV vaccine with women as per the recommendations outlined in the *Canada Communicable Disease Report, Volume 33 ACS-2, (2007) National Advisory Committee on Immunization (NACI) statement on Human Papillomavirus vaccine.*

Reporting and Partner Notification

- Infectious syphilis (primary, secondary and early latent syphilis) is reportable in all provinces and territories and notifiable to the Public Health Agency of Canada.
- Non-infectious syphilis (late latent, cardiovascular and neurosyphilis) may be reportable at the provincial/territorial level but is not notifiable to the Public Health Agency of Canada.
- All sexual or perinatal contacts within the following time periods need to be located, tested and treated if serology is reactive.

Table 5. Partner notification

Stage of syphilis	Trace-back period
Primary syphilis	3 months*
Secondary syphilis	6 months*
Early latent	1 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 sexual partner(s)
Stage undetermined	Assess/consult with a colleague experienced in syphilis management

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

- The length of time for the trace-back period should be extended:
 - 1) to include additional time up to the date of treatment
 - 2) if the index case states that there were no partners during the recommended trace back period, then the last partner should be notified
 - 3) if all partners traced (according to recommended trace-back period) test negative, then the partner prior to the trace-back period should be notified.

Follow-up

- In the absence of a test of cure, non-treponemal tests (NTTs) should be monitored until they are seronegative or at a stable low titre (e.g., $\leq 1:4$ dilutions; note however that dilutions may vary).⁵⁷
- See *Table 6* for a guide to the monitoring of NTTs.
- See *Table 7* for a guide to adequate serologic response (in NTT: e.g., RPR).⁵⁸

Table 6. Monitoring of serologic tests and other follow up

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 monthly intervals until normalization of CSF parameters (see notes below). Other clinical follow up may be indicated on a case by case basis.
HIV-infected (any stage)	(*), 3, 6, 12 and 24 months after treatment and yearly thereafter
Pregnant women with reactive syphilis serology	See <i>Table 8(a)</i>
Babies born to mothers with reactive syphilis serology	See <i>Table 8(b)</i>

(*) Some experts recommend follow up testing at 1 month after treatment to ensure that non-treponemal test titre is not rising; a rising titre may be indicative of either treatment failure or re-infection.

Table 7. Adequate serologic response

Primary	4-fold* drop at 6 months, 8-fold drop at 12 months, 16-fold drop at 24 months
Secondary	8-fold drop at 6 months and 16-fold drop at 12 months
Early latent	4-fold drop at 12 months

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

- Note that the NTT may revert to non-reactive after treatment or remain at a low steady level (e.g., $\leq 1:4$ dilutions; note however that dilutions may vary). Repeat testing is not required if the baseline or follow-up NTT becomes non-reactive, 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 re-infection, a rising NTT after treatment may indicate treatment failure or reinfection. If treatment failure is suspected, further investigation, including CSF examination, may be indicated.
- Patients with neurosyphilis and abnormal CSF examinations should have a lumbar puncture repeated at 6-month intervals after completion of treatment until CSF parameters normalize. CSF pleocytosis is generally the first measure of improvement and should occur over about 6 months.⁵⁹ Elevated protein levels, if present, will begin to decline during the first 6 months but can take up to 2 years to return to normal.⁶⁰ CSF protein may decline more slowly in patients who are neurologically abnormal compared with those who are neurologically normal.⁶¹ The CSF-VDRL titre should decline (four-fold within a year) if it is initially high, but it may take years to revert to negative.⁵⁹ A persistent, low CSF-VDRL titre after a course of treatment may warrant retreatment, but if CSF pleocytosis and elevated protein levels have resolved and serum VDRL titre has not risen, additional treatment is unlikely to be beneficial.⁶² All CSF lab parameters normalize more slowly in patients co-infected with HIV.⁶¹ The possibility of treatment failure should be considered if there is clinical progression, increase in RPR/VDRL by ≥ 2 dilutions or CSF pleocytosis fails to resolve; **treatment options for patients with treatment failure should be discussed with a colleague experienced in this area.**

Special considerations

HIV infection

- Persons co-infected with HIV may require a longer course of treatment, as well as closer and longer follow-up.

*Pregnancy*⁵⁴

- All women newly diagnosed with syphilis during pregnancy should receive treatment appropriate to their stage of disease.
- With a diagnosis of secondary syphilis in late pregnancy and despite the administration of the recommended penicillin regimen, as many as 14% will have a fetal death or deliver infants with clinical evidence of congenital syphilis.⁶³⁻⁶⁵ **This has led some experts to recommend that primary, secondary and early latent cases (due to difficulty in accurately staging cases) in pregnancy be treated with two doses of benzathine penicillin G 2.4 million units 1 week apart; the efficacy of this regimen in preventing fetal syphilis is not known.**⁵⁴
- Retreatment during pregnancy is not necessary unless there is clinical or serologic evidence of new infection (four-fold rise in a non-treponemal test titre), serologic evidence of inadequate treatment response or history of recent sexual contact with a person with infectious syphilis.
- Erythromycin is the least effective agent for the treatment of syphilis and does not penetrate the CSF or placental barrier well; it is therefore not recommended in pregnancy.^{66,67}
- Treatment of maternal syphilis can be complicated by the Jarisch-Herxheimer reaction, which can affect approximately 40% of pregnant women treated for syphilis and can be associated with uterine contractions and variable decelerations in fetal heart rate but usually resolves without incident.^{68, 69}
- Women treated for syphilis in early pregnancy should stay well hydrated and rest; acetaminophen may help uterine cramping, pelvic pain and fever.
- The risk of treatment failure increases with sonographic signs of fetal syphilis. Fetal ultrasonographic abnormalities and treatment failure in pregnancies of < 20 weeks gestation are rare. 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.⁶⁸
- If the mother is diagnosed with infectious syphilis after 20 weeks gestation, a detailed ultrasound should be performed to screen for fetal abnormalities, with the ultrasound being used as a tool to help stage the extent of fetal disease in order to assist with maternal counseling about treatment efficacy and potential complications of pregnancy.⁶⁸ If fetal abnormalities are identified (such as ascites, placental thickening, hepatomegaly)⁷⁰, the mother should be managed with an obstetric/maternal fetal specialist and should be hospitalized for treatment and fetal monitoring because some of the complications such as pre-term labour, fetal distress and stillbirth may be more common if the fetus is infected and may be precipitated by treatment.^{68,71}
- All babies should be assessed at delivery by a pediatrician or pediatric specialist (e.g., infectious diseases), and if a maternal non-penicillin regimen was used, consideration should be given to treating the baby empirically for congenital syphilis (see detailed recommendations in *Table 8b*).
- **In cases where a child is born to a mother who was diagnosed with syphilis in pregnancy, and where the child is placed under the care of child protection services, medical**

information about the mother's diagnosis may be critical to the ongoing protection and monitoring of the infant's health. It is important to facilitate the collection and disclosure of relevant health information, in accordance with provincial/territorial requirements, in order to allow appropriate follow-up care.

***Congenital syphilis*⁷² (see Table 8b)²⁸**

- Infected infants are frequently asymptomatic at birth and may be seronegative if maternal infection occurred late in gestation.



Infants should be treated at birth:

- If symptomatic.
- If the infant's non-treponemal titre is at least four-fold (2 tubes) higher than the mother's.
- If maternal treatment was inadequate, did not contain penicillin, is unknown or occurred in the last month of pregnancy, or if maternal serologic response is inadequate.
- If adequate follow-up of the infant cannot be ensured.

***Jarisch-Herxheimer reaction*^{73,74}**

- Patients should be made aware of this possible reaction to treatment, especially with penicillin.
- More common in secondary syphilis (70-90%), but can occur at any stage of infection.
- An acute febrile illness with headache, myalgia, chills, rigors which can occur as early as 2 hours after treatment and resolves within 24 hours.
- **Not clinically significant unless there is neurologic or ophthalmic involvement or in pregnancy where it may cause fetal distress and premature labour.**
- Not a drug allergy.
- Can be treated with antipyretics.
- Steroids may be indicated for the management of severe reactions but should be used in consultation with a colleague experienced in this area.

***Children* (see also *Sexual Abuse in Peripubertal and Prepubertal Children* chapter)**

- Sexual abuse must be considered when syphilis is found in children beyond the neonatal period. Consultation with a colleague experienced in the management of such cases should be sought.
- **Reporting Sexual abuse:**
Sexual abuse of children must be reported to the local child protection agency. Local public health authorities may be helpful in evaluating both the source of the infection and potential transmission in the community.
- Whenever possible, it is strongly recommended that the child be evaluated at or in conjunction with a referral centre (see *Appendix F* and *G*).
- **All persons named as suspects in child sexual abuse cases must be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat or not should be based on history, clinical findings and test results.**

Table 8(a): Summary of medical management of immunocompetent women found to have reactive syphilis serology during pregnancy

DIAGNOSIS	RISK OF TRANSMISSION (ROT) OF SYPHILIS TO FETUS	TREATMENT (see Table 3)	FURTHER ASSESSMENT AND MONITORING DURING PREGNANCY AND POST-PARTUM
Untreated infectious syphilis (primary, secondary, early latent)	<p>By stage of syphilis: Primary: 100% Secondary: 70% Early latent: 40%</p> <p>By stage of pregnancy: Risk of transmission increases as pregnancy progresses Transmission occurs as early as 9 weeks gestation, but is uncommon before 20 weeks gestation</p>	Benzathine penicillin G 2.4 million units weekly x 1-2 doses	<p>Serologic follow up (NTT) at: 1, 3, 6 and 12 months post treatment</p> <p>AND</p> <p>Monthly until delivery if at high risk of re-infection (see <i>Risk Factors</i> under <i>Diagnosis</i> section in the current chapter)</p> <p>AND</p> <p>If diagnosed with infectious syphilis at ≥ 20 weeks gestation, detailed fetal ultrasound should be performed and if fetal abnormalities consistent with congenital syphilis present, mother should be treated with fetal monitoring in place (see <i>Pregnancy</i> under the <i>Special Considerations</i> section in the current chapter)</p>
Untreated late latent syphilis	< 10%	Benzathine penicillin G 2.4 million units IM weekly x 3 doses	Serologic follow up (NTT) at time of delivery and 12 and 24 months post treatment
Previously treated	<p>Negligible if: No clinical evidence of treatment failure</p> <p>AND</p> <p>Documentation of adequate serologic response to previous treatment</p> <p>AND</p> <p>No concern about re-infection</p>	Retreatment during pregnancy is not necessary unless there is clinical or serologic evidence of new infection or history of recent sexual contact with a known case of infectious syphilis	Based on stage and time of previous treatment; additional testing may be warranted if uncertainty regarding stage of diagnosis or concerns regarding re-infection

Table 8(b): Management of infants born to women with reactive treponemal tests (TTs) during pregnancy* 28

Scenario	Baseline and monthly assessment for signs or symptoms of congenital syphilis for the first three months	Syphilis serological tests (RPR and TT) with clinical assessment each time [†]	Long-bone radiographs, complete blood cell count and differential, and sampling of CSF for cell count and differential, glucose, protein and VDRL, with a low threshold for doing ophthalmologic and audiologic assessments	Treatment for congenital syphilis
Mother has a well documented history of adequate treatment of any stage of syphilis before pregnancy, with no rise in her RPR titre during the pregnancy and no known risk factors for re-infection	No	No	No	No
Mother was treated for primary, secondary or early latent syphilis during pregnancy more than four weeks before delivery, with adequate fall in her RPR titres and no evidence of relapse or re-infection.	Yes	0, 3, 6 and 18 months	No	No
Mother was treated for late latent syphilis anytime during or following pregnancy ‡	No	0, 6, and 18 months of age	No	No

Source: Canadian Paediatric Society (Infectious Diseases and Immunization Committee, 2009). *Congenital syphilis no longer just of historic interest*. Please visit www.cps.ca/english/publications/InfectiousDiseases.htm. With permission.

CSF Cerebrospinal fluid; RPR Rapid plasma reagin; VDRL Venereal disease research laboratory

* The table assumes the maternal reactive TT result was known at or near the time of delivery. Follow-up should be performed at comparable intervals if the problem is recognized several months later;

† Rapid plasma reagin (RPR) and TTs should be repeated at recommended intervals until at least six months of age, because false-negative results could occur at zero months from transmission at delivery or at three months from partial treatment. Testing at 12 months of age or 18 months of age can be omitted if RPR and TT are both non-reactive at six months of age;

‡ Late latent syphilis implies the mother was infected more than one year before pregnancy. If there is any doubt about the stage of maternal infection, it should be assumed she may have infectious syphilis (primary, secondary, or early latent), which leads to more aggressive infant follow-up.

Table 8(b): Management of infants born to women with reactive treponemal tests (TTs) during pregnancy*²⁸ (continued)

Scenario	Baseline and monthly assessment for signs or symptoms of congenital syphilis for the first three months	Syphilis serological tests (RPR and TT) with clinical assessment each time [†]	Long-bone radiographs, complete blood cell count and differential, and sampling of CSF for cell count and differential, glucose, protein and VDRL, with a low threshold for doing ophthalmologic and audiologic assessments	Treatment for congenital syphilis
Mother had untreated primary or secondary syphilis during pregnancy, treponemes are detected on direct examination of specimens from infant, infant's RPR titre is four-fold or greater (higher than the mother's at birth), or there is a four-fold rise in the infant titre, OR child has any findings compatible with congenital syphilis at any age, OR infant has a reactive RPR (and TT) at 12 months of age or a reactive TT (confirmed with a second type of TT) at 18 months of age	Yes	0, 3, 6, and 18 months of age	Yes	Yes

Source: Canadian Paediatric Society (Infectious Diseases and Immunization Committee, 2009). *Congenital syphilis no longer just of historic interest*. Please visit www.cps.ca/english/publications/InfectiousDiseases.htm. With permission.

CSF Cerebrospinal fluid; RPR Rapid plasma reagin; VDRL Venereal disease research laboratory

* The table assumes the maternal reactive TT result was known at or near the time of delivery. Follow-up should be performed at comparable intervals if the problem is recognized several months later;

† Rapid plasma reagin (RPR) and TTs should be repeated at recommended intervals until at least six months of age, because false-negative results could occur at zero months from transmission at delivery or at three months from partial treatment. Testing at 12 months of age or 18 months of age can be omitted if RPR and TT are both non-reactive at six months of age;

Table 8(b): Management of infants born to women with reactive treponemal tests (TTs) during pregnancy*²⁸ (continued)

Scenario	Baseline and monthly assessment for signs or symptoms of congenital syphilis for the first three months	Syphilis serological tests (RPR and TT) with clinical assessment each time [†]	Long-bone radiographs, complete blood cell count and differential, and sampling of CSF for cell count and differential, glucose, protein and VDRL, with a low threshold for doing ophthalmologic and audiologic assessments	Treatment for congenital syphilis
Mother was treated for primary, secondary, or early latent syphilis within four weeks before delivery, or was treated with an antibiotic other than penicillin, OR mother was treated for primary, secondary or early latent syphilis before or during the pregnancy and her RPR titre did not show the expected decline or inadequate time has passed to assess the decline	Yes	If treated for congenital syphilis, do at 0, 3, 6 and 18 months of age; if not treated, also do at 1, 2 and 12 months of age	Yes	Usually [§]

Source: Canadian Paediatric Society (Infectious Diseases and Immunization Committee, 2009). *Congenital syphilis no longer just of historic interest*. Please visit www.cps.ca/english/publications/InfectiousDiseases.htm. With permission.

CSF Cerebrospinal fluid; RPR Rapid plasma reagin; VDRL Venereal disease research laboratory

* The table assumes the maternal reactive TT result was known at or near the time of delivery. Follow-up should be performed at comparable intervals if the problem is recognized several months later;

[†] Rapid plasma reagin (RPR) and TTs should be repeated at recommended intervals until at least six months of age, because false-negative results could occur at zero months from transmission at delivery or at three months from partial treatment. Testing at 12 months of age or 18 months of age can be omitted if RPR and TT are both non-reactive at six months of age;

[§] May choose to follow closely if all investigations are normal and infant follow-up can be assured, but treatment for congenital syphilis would be the preferred option as the risk is significant.

Table 8(b): Management of infants born to women with reactive treponemal tests (TTs) during pregnancy*²⁸ (continued)

Scenario	Baseline and monthly assessment for signs or symptoms of congenital syphilis for the first three months	Syphilis serological tests (RPR and TT) with clinical assessment each time [†]	Long-bone radiographs, complete blood cell count and differential, and sampling of CSF for cell count and differential, glucose, protein, and VDRL, with a low threshold for doing ophthalmologic and audiologic assessments	Treatment for congenital syphilis
Mother was treated for primary, secondary or early latent syphilis before pregnancy, but there are doubts about the adequacy of therapy or the possibility of re-infection OR mother was treated for primary, secondary or early latent syphilis during pregnancy and her follow-up RPR was not obtained OR mother was treated for any type of syphilis during pregnancy but long-term infant follow-up cannot be assured	Yes	If treated for congenital syphilis, do at 0, 3, 6, and 18 months of age; if not treated, also do at 1, 2, and 12 months of age	Depends on risk, but mandatory if mother had primary, secondary, or early latent syphilis and follow-up is not likely to occur, or if clinical or serologic findings are abnormal	Depends on risk and on results of assessments [¶]
Infant has a reactive RPR (and TT) at six months of age	NA	Depends on timing of last serology	Yes	Usually**

Source: Canadian Paediatric Society (Infectious Diseases and Immunization Committee, 2009). *Congenital syphilis no longer just of historic interest*. Please visit www.cps.ca/english/publications/InfectiousDiseases.htm. With permission.

CSF Cerebrospinal fluid; NA Not applicable; RPR Rapid plasma reagin; VDRL Venereal disease research laboratory

* The table assumes the maternal reactive TT result was known at or near the time of delivery. Follow-up should be performed at comparable intervals if the problem is recognized several months later;

† Rapid plasma reagin (RPR) and TTs should be repeated at recommended intervals until at least six months of age because false-negative results could occur at zero months from transmission at delivery or at three months from partial treatment. Testing at 12 months of age or 18 months of age can be omitted if RPR and TT are both non-reactive at six months of age;

¶ If it seems likely the mother was adequately treated, the risk of maternal reinfection is low, and infant follow-up can be assured, or if the mother had late latent syphilis, serologic follow-up is sufficient. If any of these criteria are not met, full evaluation and treatment should be considered;

** Assuming all assessments are normal, this infant may not have congenital syphilis. It is possible the reactive RPR is passive, but treatment would be the preferred option because of the significant chance the infant has congenital syphilis.