



This optimal usage guide is provided for information purposes only and should not replace the judgment of a professional. The recommendations included in this guide apply to adolescents aged 14 and over and to adults. This guide has been adapted from the original document of the Agence de la santé et des services sociaux des Laurentides by a committee of experts.

GENERAL CONSIDERATIONS

- ▶ A resurgence of infectious syphilis has been observed in Québec; though infectious syphilis had practically disappeared by the late 1990s, several hundred cases are now being reported each year. This resurgence mainly affects men who have sex with men (MSM).
- ▶ The number of reported cases of infectious syphilis in women of childbearing age has also risen noticeably since 2009. For the first time since the early 2000s, a documented case of congenital syphilis in a baby born to a Quebecer mother was reported in 2011. Another case of congenital syphilis was reported in 2012. **Close vigilance is required from all professionals.**
- ▶ **For the treatment of pregnant or nursing women, consult an experienced colleague.**

ETIOLOGY

Syphilis is a bacterial infection caused by *Treponema pallidum* subspecies *pallidum*.

TRANSMISSION

- **The highest risk is by vaginal, anal or orogenital sexual contact, with or without penetration**
- By transmission from an infected mother to her baby via the placenta or during childbirth
- By direct contact with cutaneous or mucosal lesion exudate
- By indirect contact (e.g. sex toys)
- Less common modes of transmission:
 - By blood transfusion when transfusion safety measures are not in place (e.g. in some foreign countries)
 - When injection supplies are shared

Syphilis is said to be “infectious” when contagion is the strongest, that is, during the primary, secondary and early latent stages. These stages correspond to the first year of the illness.

SCREENING

- ▶ In addition to completing diagnostic laboratory analyses for all individuals exhibiting signs and symptoms consistent with syphilis, **the following individuals should also be screened for syphilis:**
 - **Any asymptomatic person presenting risk factors** (see the tool titled *Tableau sur les ITSS à rechercher selon les facteurs de risque décelés* at the following URL: www.msss.gouv.qc.ca/its, **Documentation** section, under **Professionnels/outils** [French only])
 - **All pregnant women** at their first prenatal visit (systematic screening). Screening should be repeated at least once at approximately 28 weeks' gestation and at delivery if:
 - New exposure is suspected
 - High-risk behaviours continue
 - A partner presents one or more risk factors

GENERAL CONSIDERATIONS

CLINICAL MANIFESTATIONS

- ▶ Left untreated, syphilis can evolve in three clinical stages: primary, secondary and tertiary. **The primary and secondary stages may go unnoticed.** Latent syphilis is an asymptomatic stage that occurs between the secondary and tertiary stages.
- ▶ Syphilis is often called “the great imitator” because its clinical manifestations are often confused with other illnesses, particularly in the secondary and tertiary stages of the illness.

	STAGE	MOST COMMON CLINICAL MANIFESTATIONS
INFECTIOUS PERIOD	PRIMARY Occurs after an incubation period of 10–90 days, 3 weeks on average	A chancre A superficial ulcer, firm, with a regular outline, size may vary, painless (unless a secondary bacterial infection exists) Localized to inoculation site: genital, anorectal or oropharyngeal area Most often a single ulcer Regional adenopathy Spontaneous regression in 3–6 weeks Most frequent differential diagnoses Herpes, lymphogranuloma venereum (less common)
	SECONDARY Occurs 4–10 weeks, sometimes several months, after the chancre appears	Diffuse rash Most often maculopapular in nature, although may take other forms May include the palm of the hand and the sole of the foot Other possible manifestations: <i>condyloma lata</i> , alopecia, uveitis, retinitis, meningitis, hepatitis Spontaneous regression in 3–12 weeks followed by beginning of latent phase Influenza-like illness Fever, headache, myalgia, arthralgia, fatigue with or without widespread adenopathy Most frequent differential diagnoses Mononucleosis syndrome, primary infection by HIV
	EARLY LATENT SYPHILIS Infection acquired within the last year	No clinical manifestation Diagnosis relies on serologic analyses and clinical history Considered early if history and serology indicate the infection was acquired within the last year The infection can be transmitted even when the infected person is asymptomatic
NON-INFECTIOUS PERIOD	LATE LATENT SYPHILIS Infection acquired over a year ago	No clinical manifestation Diagnosis relies on serologic analyses and clinical history Considered late if history and serology do not indicate the infection was acquired within the last year
	TERTIARY Appears on average 5–30 years after the infection was acquired	Various forms exist Left untreated, this illness may evolve into the tertiary stage Cardiovascular syphilis: aortic aneurysm, aortic regurgitation, etc. Gummatous syphilis: mainly cutaneous and osteoarticular lesions Neurosyphilis: vertigo, personality changes, dementia, gait disturbance, Argyll Robertson pupil, loss of vibration sense, etc.
	CONGENITAL SYPHILIS	Risk of transmission highest among pregnant women with untreated infectious syphilis Manifests as: sniffles, hepatosplenomegaly, adenopathy, mucocutaneous lesions, pneumonia, osteochondritis, skin eruptions, hemolytic anemia or thrombocytopenia Often asymptomatic 40% of pregnancies among untreated infected women result in stillbirth



SYPHILIS

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LABORATORY ANALYSIS

- ▶ Laboratories can begin serologic analysis with either a non-treponemal (RPR) or a treponemal test (EIA or CIA).
 - **Non-treponemal test results** can be qualitative or quantitative (titre). Obtaining a quantitative result allows the practitioner to:
 - Help identify the stage of infection
 - Monitor response to treatment
 - Detect a new episode
 - **Treponemal test results** are qualitative.
- ▶ The main criteria for **lumbar puncture** for CSF analysis (cell count, protein, glucose and VDRL) are:
 - Presence of neurologic or ophthalmic signs or symptoms
 - Previously treated patients who fail to exhibit adequate serologic response to treatment
 - Tertiary syphilis
 - Suspected congenital syphilis
- ▶ Direct treponemal observation with cutaneous or mucosal lesion samples under **dark-field microscopy** is not widely available.

SYPHILIS SERODIAGNOSTIC INTERPRETATION TABLE

RESULTS FROM SEROLOGIC ANALYSIS			INTERPRETATION
EIA or CIA	RPR	CONFIRMATION TEST RESULTS ¹	
N/A	Non-reactive	N/A	1) No treponematosi s (no syphilis). 2) If incubating syphilis is suspected, draw a second serum sample three months after the presumed contact. 3) If primary syphilis is suspected, draw a second serum sample 2–4 weeks after the onset of symptoms. 4) If secondary syphilis is suspected, notify the laboratory so that the possibility of a prozone effect ² can be evaluated.
Non-reactive	N/A		
N/A	Reactive (All dilutions)	Reactive	Syphilitic treponematosi s; clinical manifestation and treatment history information is required to refine the interpretation: <ul style="list-style-type: none"> a) Infectious syphilis: primary, secondary or early latent b) Late latent syphilis c) Tertiary syphilis d) Treated syphilis with persistent reactive RPR
Reactive	Reactive (Dilutions \geq 1:8)	N/A	
Reactive	Reactive (Dilutions 1:1 to 1:4)	Reactive	
Reactive	Non-reactive	Reactive	1) Syphilitic treponematosi s; clinical manifestation and treatment history information is required to refine the interpretation: <ul style="list-style-type: none"> a) Primary syphilis before RPR seroconversion b) Secondary syphilis with RPR prozone effect² c) Late latent syphilis after RPR seroreversion d) Treated syphilis 2) Non-syphilitic treponematosi s possible (bejel, yaws or pinta)
N/A	Reactive (All dilutions)	Non-reactive	1) No treponematosi s; RPR ³ and/or EIA/CIA ⁴ falsely reactive. 2) If incubating or primary syphilis is suspected, draw a second serum sample in 2–4 weeks.
Reactive	Non-reactive or reactive (Dilutions 1:1 to 1:4)		

CIA : chemiluminescence immunoassay; EIA: enzyme immunoassay; RPR: rapid plasma reagin
 N.A. : not applicable

1. Depending on the serologic profile, confirmation tests will include TP-PA, with or without INNO-LIA.
2. In vitro RPR phenomenon in which a sample with a high concentration of antibodies provides false negative results.
3. Some causes of false positive RPR results include certain collagen diseases, pregnancy, injection drug use and other infections.
4. Some causes for false positive EIA or CIA results include other infections, including other spirochete infections such as borreliosis (Lyme disease) or leptospirosis.



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TREATMENT PRINCIPLES

- ▶ **The treatment of choice is benzathine penicillin G (Bicillin™ L-A).**
- ▶ **Refer to the *Canadian Guidelines on Sexually Transmitted Infections* and consult an experienced colleague before treating pregnant women, congenital syphilis, meningitis, ocular involvement and tertiary syphilis.**
- ▶ **For the treatment of syphilis in HIV-infected patients, initiate treatment according to the stage of infection in the treatment table below AND direct patients to an experienced colleague within one week, in order to determine what medical follow-up is appropriate (medical workup, treatment, serologic follow-up).**
- ▶ The **Jarisch-Herxheimer reaction** is possible following a **benzathine penicillin G** injection. It is an acute febrile illness that:
 - Generally occurs within 2 hours of receiving a penicillin injection and resolves within 24 hours
 - Is often accompanied by headaches and myalgia
 - Is more commonly associated with secondary syphilis but may occur at any stage of infection
 - Is generally not clinically significant unless the patient experiences neurologic or ophthalmic symptoms, or is pregnant
 - May be symptomatically treated with antipyretics (acetaminophen/NSAIDs)
- ▶ Considering reports of treatment failure and resistance development, azithromycin is not recommended for the treatment of syphilis in infected patients or their partners.

RECOMMENDED TREATMENT¹

STAGE	ANTIBIOTIC OF CHOICE ²	IF ALLERGY TO PENICILLIN ²
ADULTS AND ADOLESCENTS AGED 14 AND OVER		
Primary Secondary Early latent	Benzathine penicillin G (Bicillin™ L-A) 2.4 million units, IM, in a single dose	Doxycycline³ (Vibramycine™) , 100 mg, orally, twice a day for 14 days OR FOLLOWING DESENSITIZATION: Benzathine penicillin G (Bicillin™ L-A) 2.4 million units, IM, in a single dose
Late latent Latent of unknown duration	Benzathine penicillin G (Bicillin™ L-A) 2.4 million units, IM, weekly for 3 doses	FOLLOWING DESENSITIZATION: Benzathine penicillin G (Bicillin™ L-A) 2.4 million units, IM, weekly for 3 doses OR Doxycycline³ (Vibramycine™) , 100 mg, orally, twice a day for 28 days
PREGNANT OR NURSING WOMEN		
Primary Secondary Early latent Late latent Latent of unknown duration	Initiate treatment with one dose of benzathine penicillin G (Bicillin™ L-A) , 2.4 million units, IM AND Refer the woman to an experienced colleague within one week to evaluate the need for further treatment	Refer the woman to an experienced colleague within one week AND Treatment with benzathine penicillin G (Bicillin™ L-A) , after desensitization, should be preferred

1. The order in which antibiotics are presented takes into account efficacy and safety data, antibiotic resistance, ease of administering the regimen and cost.
2. Only one brand name is provided, although several manufacturers may offer products under other brand names. A variety of generic versions are also available.
3. This product is recommended in the *Canadian Guidelines on Sexually Transmitted Infections*, although it has not received approval from Health Canada for this purpose.

POST-TREATMENT SEROLOGIC FOLLOW-UP

- ▶ Treatment response is evaluated based on the **clinical picture** and a **decrease in non-treponemal test titres**.
- ▶ **Clinical and serologic testing** should be completed for all treated patients until an adequate response is exhibited, in line with the following table.

STAGE	RPR FREQUENCY	DESIRED RESPONSE
Primary syphilis	3, 6 and 12 months after treatment	4-fold drop ¹ after 6 months 8-fold drop after 12 months
Secondary syphilis	3, 6 and 12 months after treatment	8-fold drop after 6 months 16-fold drop after 12 months
Early latent syphilis	3, 6 and 12 months after treatment	4-fold drop after 12 months
Late latent, tertiary syphilis (with the exception of neurosyphilis)	12 and 24 months after treatment	Consult an experienced colleague
Neurosyphilis	6, 12 and 24 months after treatment	
Co-infection with HIV	3, 6, 12 and 24 months after treatment, then annually	
Congenital syphilis	Refer to the <i>Canadian Guidelines on Sexually Transmitted Infections</i>	

1. 4-fold drop = 2-dilution drop (e.g., change from 1:32 dilutions to 1:8 dilutions)

- ▶ A significant titre increase (a 2-dilution or 4-fold titre increase, e.g., change from 1:2 to 1:8), or an overly small decrease may indicate treatment failure or a new episode; the patient should be re-evaluated.
- ▶ Remember that dilutions progress as follows: 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, etc.
- ▶ Titres should be monitored until they become negative or low and stable (e.g., 1:4 or less).



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MANAGEMENT



SYPHILIS

Free access to prescribed medication

- For person registered for the health insurance plan who has a valid health insurance card, claim slip or temporary proof of eligibility for medication AND
- If the code K (for the infected patient) or L (for partners) is written on the prescription

Intervention with the infected patient

- ▶ Management must include **adequate treatment and follow-up** for the infected patient as well as **a procedure for the notification and treatment of sexual partners**
- ▶ **In regard to sexual relations in a case of infectious syphilis:**
 - **Recommend abstinence from sexual relations** for up to 7 days following the end of penicillin treatment or until the end of doxycycline treatment AND
 - **Recommend abstinence from sexual relations** until symptoms indicating potentially infectious lesions are resolved AND
 - After the period of abstinence, recommend using condoms for all types of sexual relations (vaginal, anal or orogenital) at least until the results of screening tests for other STBBIs are known

Interventions with sexual partners

- ▶ Immediate **epidemiological treatment** (treatment when laboratory analysis results are unknown or negative) with a single IM injection of 2.4 million units of benzathine penicillin G is always recommended:
 - For partners who have had sexual contact in the last 90 days with a case of infectious syphilis (primary, secondary or early latent)
 - For partners who have had sexual contact more than 90 days ago with a case of infectious syphilis (primary, secondary or early latent) if follow-up is uncertain
 - For sexual partners of cases of late latent syphilis with RPR titre above 1:32, an approach similar to sexual partners of cases of infectious syphilis should be taken (see the two previous bullet points)
- ▶ **The following people should be contacted and screened:**

STAGE	PEOPLE TO CONTACT AND SCREEN
PRIMARY	<p>People who had sexual relations with the infected person:</p> <p>Up to 3 months before the infected person began experiencing symptoms</p> <p>Up to 4 months and 1 week before samples were taken, if the date that symptoms began is unknown or uncertain</p> <p>While symptoms were present</p> <p>Before the end of treatment or less than 7 days after a single-dose treatment</p>
SECONDARY	<p>People who had sexual relations with the infected person:</p> <p>Up to 6 months before the infected person began experiencing symptoms</p> <p>Up to 8 months before samples were taken, if the date that symptoms began is unknown or uncertain</p> <p>While symptoms were present</p> <p>Before the end of treatment or less than 7 days after a single-dose treatment</p>
EARLY LATENT	<p>People who had sexual relations with the infected person:</p> <p>Up to 1 year before samples were taken from the infected person</p> <p>Before the end of treatment or less than 7 days after a single-dose treatment</p>
LATE LATENT AND TERTIARY	<p>Current partners</p> <p>Past partners who had a long-term relationship with the infected person</p> <p>In cases of late latent syphilis with titre concentrations above 1:32, it is safer to seek out every partner from the last year.</p>
ALL STAGES	<p>Children:</p> <p>When a woman is diagnosed with syphilis, past pregnancies and the possibility that she was infected at that time should be explored. Children should be screened as necessary.</p>

- ▶ **Individuals who are screened and whose laboratory results are positive will need to be treated.** Interventions with these individuals will need to include a procedure to notify their sexual partners.
- ▶ The regional public health department may provide clinicians with information about the support available for notifying partners and referring them to competent resources for clinical evaluation, laboratory analyses, treatment and health education.

Mandatory reporting

- ▶ Syphilis must be reported to the regional public health department as it is a **notifiable disease**.



When a person consults a medical practitioner, for instance about STBBIs or contraception or for a routine examination, the practitioner should:

- **ASSESS RISK FACTORS** for STBBIs and **SCREEN** as necessary, as many people are asymptomatic and ignore that they are infected
- **INFORM** the person about safer sexual practices and encourage consistent use
- **VACCINATE** against hepatitis and the human papillomavirus as indicated in the Protocole d'immunisation du Québec (chapter 10.4)

Family physicians can use procedure code No. 15230 for STBBI-related preventive interventions.

A variety of STBBI-related tools directed at health professionals are available:

- *Intervention préventive relative aux ITSS : outil d'aide à la pratique, visite initiale et visite subséquente*
- *Tableau sur les ITSS à rechercher selon les facteurs de risque décelés*
- *Prélèvements et analyses recommandés en fonction de l'infection recherchée chez les personnes asymptomatiques*
- *Les partenaires sexuels, il faut s'en occuper! – Aide-mémoire à l'intention des professionnels de la santé*

These tools can be found on the following website: go to www.msss.gouv.qc.ca/itss, in the Documentation section, under Professionnels/outils.

REFERENCES

Public Health Agency of Canada (PHAC). Canadian Guidelines on Sexually Transmitted Infections. Ottawa, ON: PHAC; 2010.

Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. Atlanta, GA: CDC, U.S. Department of Health and Human Services; 2010.

Institut national de santé publique du Québec (INSPQ). Mise à jour des algorithmes de sérodiagnostic de la syphilis. Québec, QC: INSPQ; 2016.

Institut national de santé publique du Québec (INSPQ). Analyses de laboratoire recommandées pour le dépistage de la syphilis. Québec, QC: INSPQ; 2015.

Ministère de la Santé et des Services sociaux (MSSS). Guide québécois de dépistage des infections transmissibles sexuellement et par le sang. Québec, QC: MSSS; updated in 2016.

Ministère de la Santé et des Services Sociaux (MSSS). Les partenaires sexuels, il faut s'en occuper!. Québec, QC: MSSS; updated in 2016.