

GENERAL CONSIDERATIONS

CLINICAL MANIFESTATIONS

- ▶ Left untreated, syphilis develops in three clinical stages: primary, secondary and tertiary. **The primary and secondary stages may go unnoticed.** Latent syphilis is an asymptomatic period 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 Appears after an incubation period of 3-90 days (3 weeks on average)	<p>A chancre A superficial ulcer, firm, with a regular outline, size may vary, painless (unless bacterial secondary infection exists) Localized to inoculation site: genital, anorectal or oropharyngeal area Most often a single ulcer Regional adenopathy Spontaneous regression in 3-8 weeks</p> <p>Most frequent differential diagnoses Herpes, lymphogranuloma venereum (less common)</p>
	SECONDARY Appears 2-12 weeks, sometimes several months, after the chancre has healed	<p>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: flat condyloma, alopecia, uveitis, retinitis, meningitis Spontaneous regression in 3-12 weeks followed by beginning of latent phase</p> <p>Influenza-like illness Fever, headache, myalgia, arthralgia, fatigue with or without widespread adenopathy</p> <p>Most frequent differential diagnoses Mononucleosis syndrome, primary infection by HIV</p>
	EARLY LATENT SYPHILIS Infection acquired within the last year	<p>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</p>
NON-INFECTIOUS PERIOD	LATE LATENT SYPHILIS Infection acquired over a year ago	<p>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</p>
	TERTIARY Appears on average 5-30 years after the chancre has healed	<p>Various forms exist Left untreated, this illness may evolve into the tertiary stage</p> <p>Cardiovascular syphilis: aortic aneurysm, aortic regurgitation, etc.</p> <p>Syphilitic gumma: mainly cutaneous and osteoarticular lesions</p> <p>Neurosyphilis: vertigo, personality changes, dementia, gait disturbance, Argyll Robertson pupil, loss of vibration sense, etc.</p>
	CONGENITAL SYPHILIS	<p>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 May be asymptomatic 40% of pregnancies among infected, untreated women result in stillbirth</p>

INESSS
LE SAVOIR PREND FORME

JANUARY 2012
PHARMACOLOGICAL TREATMENT
STBBI

SYPHILIS

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 an experts committee.

GENERAL CONSIDERATIONS

- ▶ A resurgence of infectious syphilis has been observed in Québec since the early 2000s, with a more than 10-fold increase in incidence and the number of cases between 2002 and 2010. 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 in 10 years, a documented case of congenital syphilis in a baby born in Québec to a Quebecer mother was reported in 2011. **Vigilance on the clinician’s part is important.**
- ▶ **For the treatment of pregnant or nursing women, consult an experienced colleague.**

ETIOLOGY

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

TRANSMISSION

- **The highest risk is by vaginal, anal or orogenital sexual contact, with or without penetration**
- By transplacental transmission from a mother to her fetus
- 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 analysis 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** (consult the tool named *Tableau sur les ITSS à rechercher selon les facteurs de risque décelés* available at www.msss.gouv.qc.ca/its, in the **Documentation section under Professionals/outils**).
 - **All pregnant women** at their first prenatal visit (systematic screening). Screening should be repeated at least again 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.

When a person consults a clinician, for instance about STBBIs, contraception or during a periodic examination, the clinician should:

- **ASSESS RISK FACTORS** for STBBIs and **SCREEN** according to indications, since many persons are asymptomatic and unaware that they are infected;
- **INFORM** the person of 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*

Those tools can be consulted at www.msss.gouv.qc.ca/its, in the **Documentation section under Professionals/outils**.

PHARMACOLOGICAL TREATMENT
STBBI

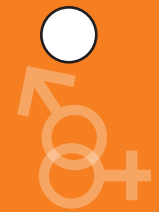
REFERENCES

- 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). Rapport du sous-comité Épreuves de détection de la syphilis. Québec, QC: INSPQ; 2009.
- Ministère de la Santé et des Services sociaux (MSSS). Guide québécois de dépistage des infections transmissibles sexuellement et par le sang. Québec, QC: MSSS; 2006.
- Ministère de la Santé et des Services sociaux (MSSS). Intervention préventive auprès des personnes atteintes d’une infection transmissible sexuellement et auprès de leurs partenaires. Aide-mémoire à l’intention des professionnels de la santé. Québec, QC: MSSS; 2010.

This guide was prepared in collaboration with the Institut national de santé publique du Québec, the ministère de la Santé et des Services sociaux and various experts in the field. It has the support of the professional orders (CMQ, OPQ, OIIQ), the federations (FMOQ, FMSQ), and various associations of Québec physicians and pharmacists. Any reproduction of this document in whole or in part for non-commercial use is permitted on condition that the source is mentioned.

Québec

**Institut national
d’excellence en santé
et en services sociaux**
Québec



LABORATORY ANALYSIS

- Laboratories can begin serologic analyses with either a non-treponemal (RPR) or a treponemal (EIA or CIA) test.
 - Non-treponemal test** results can be qualitative or quantitative (titre). Getting 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 primary criteria for **lumbar puncture** for CSF analysis (cell count, proteins, 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
RPR	EIA or CIA	CONFIRMATION TEST RESULTS ¹	
Non-reactive	N/A	N/A	1) No treponematosi (no syphilis). 2) If incubated or primary syphilis is suspected, take a second serum sample 2-4 weeks later. 3) If secondary syphilis is suspected, advise the laboratory so that the possibility of a prozone effect ² can be evaluated.
N/A	Non-reactive		
Reactive (Dilutions may vary)	N/A	Reactive	Syphilitic treponematosi; clinical manifestation and treatment history information is required to refine the interpretation: a) Infectious syphilis: primary, secondary or early latent; b) Late latent syphilis; c) Tertiary syphilis; d) Treated syphilis with persistent reactive RPR.
	Reactive	N/A	
Non-reactive	Reactive	Reactive	1) Syphilitic treponematosi; clinical manifestation and treatment history information is required to refine the interpretation: a) Primary syphilis before RPR seroconversion; b) Secondary syphilis with RPR prozone effect ² ; c) Late latent syphilis after RPR seroconversion; d) Treated syphilis. 2) Non-syphilitic treponematosi possible (bejel, yaws or pinta).
Reactive	N/A	Non-reactive	1) No treponematosi, RPR ³ or EIA/CIA ⁴ falsely reactive. 2) If incubated or primary syphilis is suspected, take a second serum sample 2-4 weeks later.
Non-reactive	Reactive		

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 certain viral infections.
 4. Some causes of false positive EIA or CIA results include other spirochete infections such as borreliosis (Lyme disease) or leptospirosis.

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 for treatment of 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	Doxycycline ³ (Vibramycin™), 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 Doxycycline ³ (Vibramycin™), 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 Penicillin desensitization followed by treatment with benzathine penicillin G (Bicillin™ L-A) should be strongly considered.

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 titre 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).

MANAGEMENT

Free access to prescribed medication

- For people who have a valid health insurance card
- 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 and a **procedure to notify and treat sexual partners**.
- In regard to sexual relations:**
 - 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 STBBI are known.

Interventions with sexual partners

- Immediate **epidemiologic 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 cases of infectious syphilis, or cases of late latent syphilis with a titre of 1:32 or greater: treat all sexual partners exposed within the last 90 days, OR
 - For cases where the follow-up of an identified sexual partner cannot be assured: treat the partner regardless of the date of contact.

- The following **people should be contacted and screened**:

STAGE	PEOPLE TO CONTACT AND SCREEN
PRIMARY	People who had sexual relations with the infected person: Up to 3 months before the infected person began experiencing symptoms Up to 4 months and 1 week before diagnosis, if the date that symptoms began is unknown or uncertain While symptoms were present
SECONDARY	People who had sexual relations with the infected person: Up to 6 months before the infected person began experiencing symptoms Up to 8 months before diagnosis, if the date that symptoms began is unknown or uncertain While symptoms were present
EARLY LATENT	People who had sexual relations with the infected person: Up to 1 year before the infected person was diagnosed
LATE LATENT AND TERTIARY	Current partners Past partners who had a long-term relationship with the infected person
ALL STAGES	Children: 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.

- 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**.