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Canada

Let’s talk about syphilis

A case-based clinical overview

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NOTE: This presentation includes graphic images of syphilis clinical examination findings.

Introduction

- Medical Advisor in Sexually Transmitted and Blood-Borne Infections Surveillance Division at PHAC
- Certified in Family Medicine and holds a Master of Public Health degree
- Extensive clinical experience in the assessment of management of syphilis
- Involved in multidisciplinary projects related to syphilis

Disclosure

Presenter: Andrea Chittle

- Relationships with financial sponsors:
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  - Patents: N/A
  - Other: Employee of the Public Health Agency of Canada

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Objectives

After attending this presentation, participants will be able to:

1. Recall, refer to, and implement national screening and treatment recommendations for syphilis.
2. Explain the role of epidemiologic information, clinical exam findings, and the interpretation of test results in the diagnosis of syphilis.
3. Support the treatment and follow-up of individuals diagnosed with syphilis infections using national clinical recommendations.

Overview

01

Background

Trends in infectious and congenital syphilis in Canada

02

Syphilis case 1: Ana

Prenatal sexually transmitted infections (STI) screening and infectious syphilis in pregnancy

03

Syphilis case 2: Kris

Latent syphilis of unknown duration

01 BACKGROUND

Trends in infectious and congenital syphilis in Canada

Poll question #1

TRUE

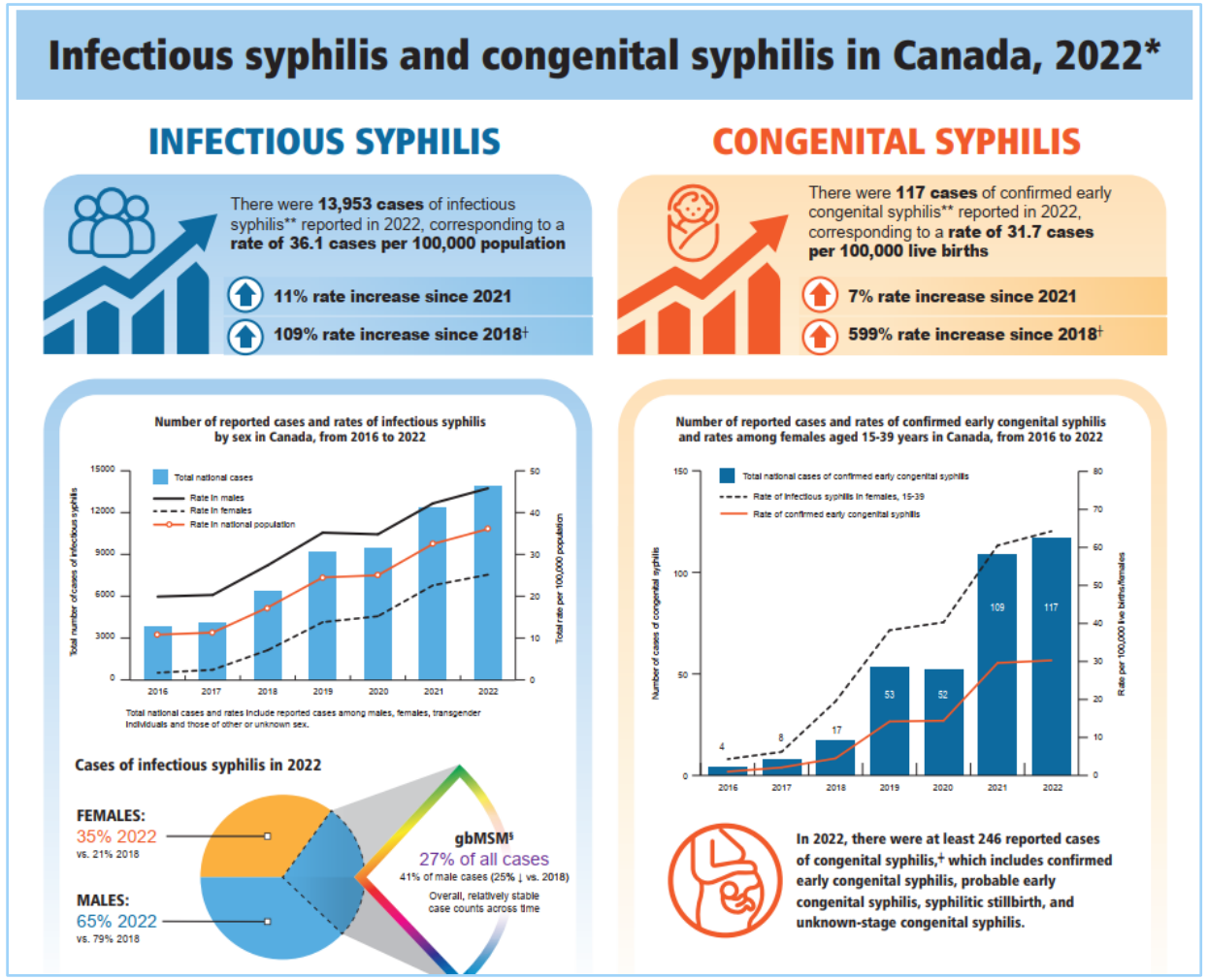
OR

FALSE

In recent years in Canada, rates of infectious syphilis have been rising more rapidly among males compared to females.

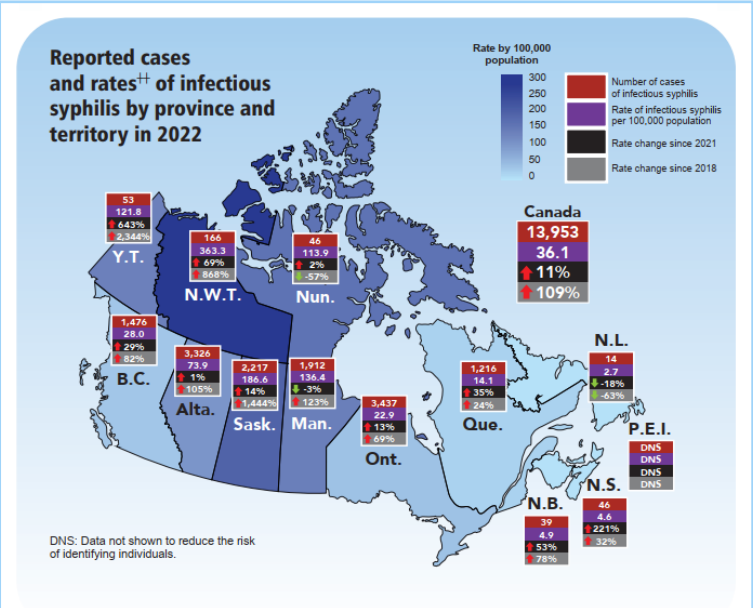
Infectious and congenital syphilis in Canada

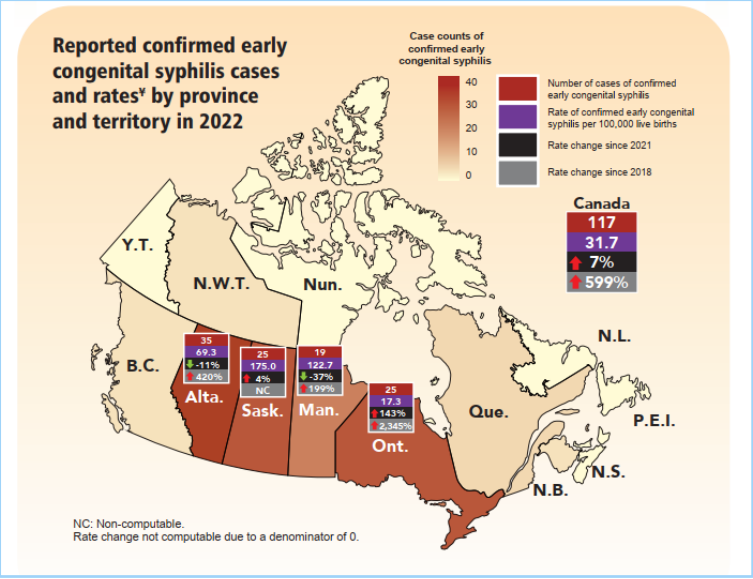
- Infectious syphilis rates have been rising since the early 2000s
- From 2013 - 2022, the rate of infectious syphilis increased almost **4-fold among males** and more than **31-fold among females**
- Increases in syphilis among reproductive-age females have corresponded with dramatic increases in congenital syphilis



(PHAC, 2022; PHAC, 2023a)

Infectious and congenital syphilis in Canada





- The prairie provinces and territories are disproportionately burdened
- From 2017 – 2020, rates of positive direct syphilis tests (i.e., PCR) in Manitoba increased more rapidly in rural compared with urban settings
  - Rates of infectious syphilis increased more than 38-fold in rural regions and more than 7-fold in urban regions
- Social and structural determinants contribute to inequities

(Tsang et al, 2022; PHAC, 2023a; PHAC, 2023b)

SYPHILIS CASES

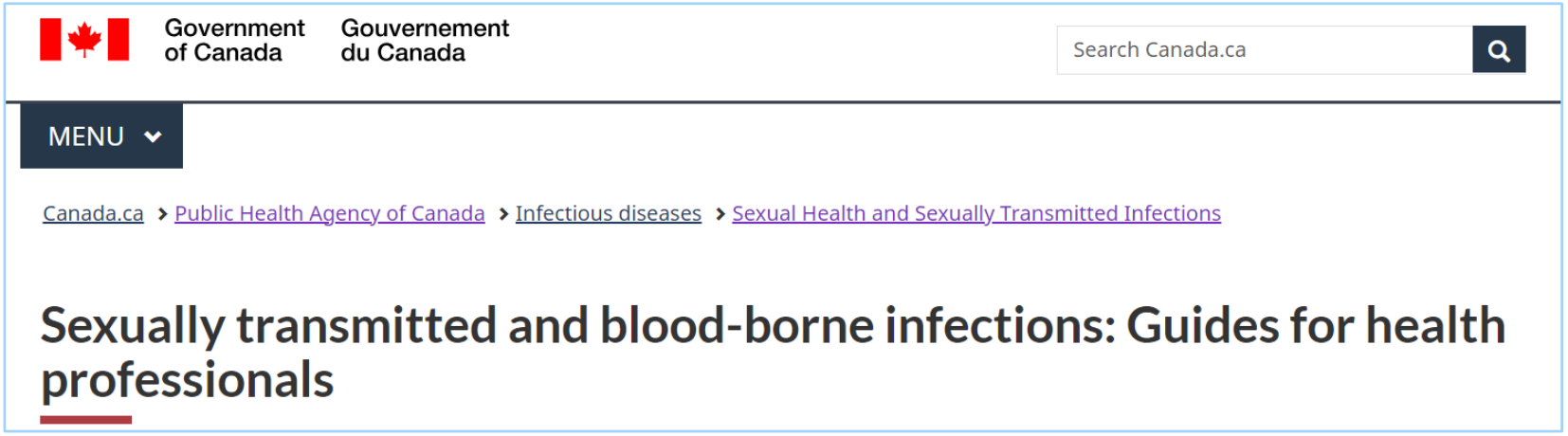
Where to find PHAC's syphilis recommendations

PHAC's evidence-based STBBI recommendations can be found:

Online [STBBI: Guides for Health Professionals webpage on Canada.ca]

Mobile CDN STBBI Guidelines mobile app

Available on the App store or Google Play

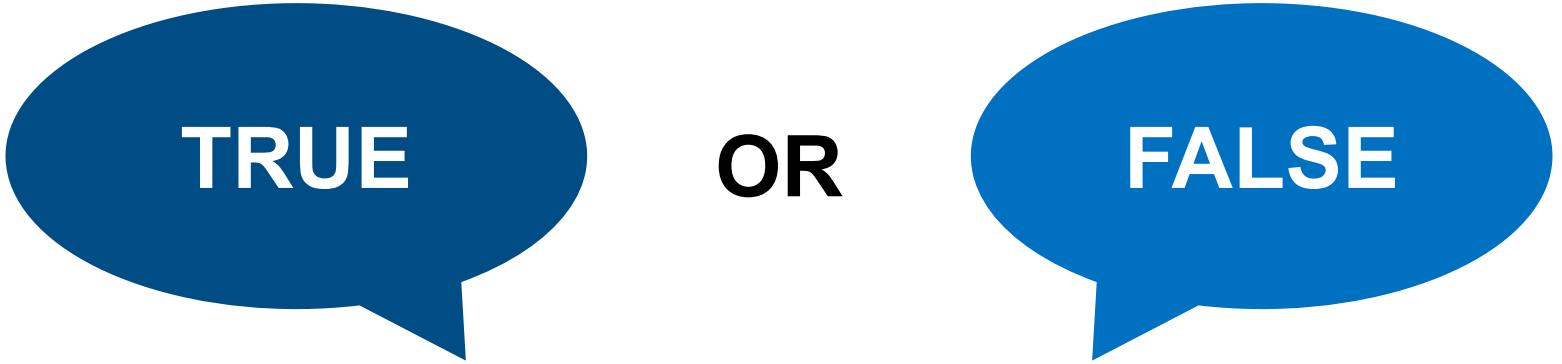


STI ITS Canada

02 CASE 1: Ana

Prenatal STI screening and infectious syphilis in pregnancy

Poll question #2



If there are discrepancies between provincial/territorial/local guidelines and PHAC guidelines for STI care, clinicians should follow provincial/territorial/local guidelines.

Case 1: Ana

Patient information

- 21-year-old cisgender woman

Reason for visit

- Presents for first prenatal visit
- Gestational age by last menstrual period: 7 weeks + 1 day

Medical history

- No significant past medical or surgical history
- No medications
- No known drug allergies

Poll question #3

According to PHAC's STBBI: Guides for Health Professionals, when should pregnant individuals be screened for syphilis?

A. During the first trimester or at the first prenatal visit

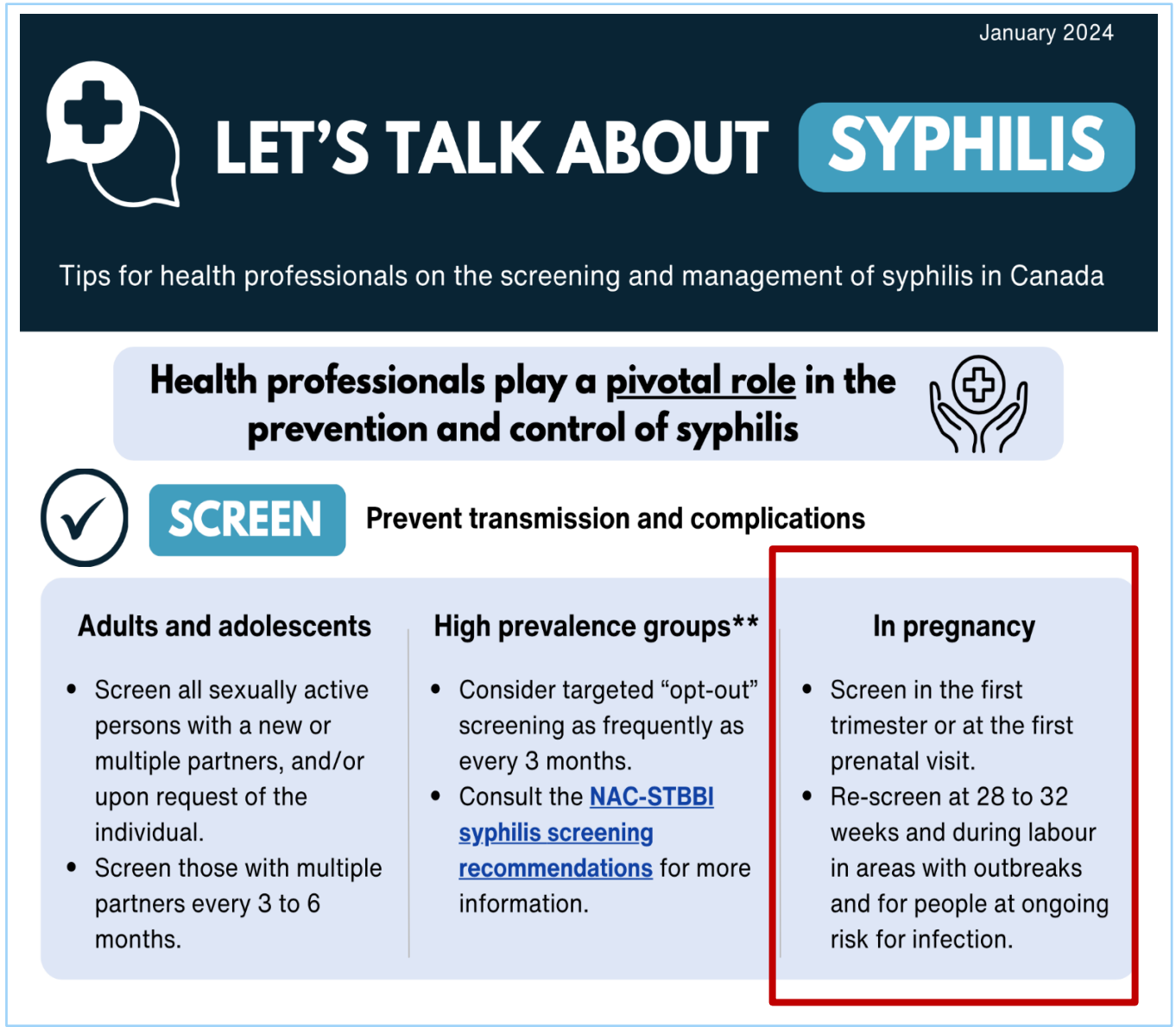
B. At 28-32 weeks if at ongoing risk and in areas experiencing outbreaks

C. At delivery if at ongoing risk and in areas experiencing outbreaks

D. More frequently if at ongoing risk

E. All of the above

Syphilis screening in pregnancy



(PHAC, 2024a)

Case 1: Ana

Investigations:

Test	Source	Result
Treponema pallidum CMIA	Serum	Non-reactive

Acronyms: CMIA: Chemiluminescent microparticle immunoassay

[8 years later] Case 1: Ana[1]

Patient information

- 29-year-old cisgender woman

Reason for visit

- Presents to care as a syphilis contact
- Pregnant with uncertain last menstrual period and no antenatal care in this pregnancy

Medical history

- G4P3; 3 previous term infants were delivered by spontaneous vaginal delivery
- No significant past medical or surgical history
- No medications
- No known drug allergies

[1] Modified from Rosenthal & Poliquin, 2022

Poll question #4

What are some possible signs of syphilis?

A. Lymphadenopathy

B. Skin rash involving the palm and soles

C. Diastolic murmur

D. Personality change

E. A - D can all occur with a syphilis infection

Case 1: Ana[1]

- Has not noticed any signs or symptoms of syphilis
- Physical exam is remarkable for:
  - Painless, shallow ulcerated vulvar lesion at the posterior fourchette
  - Uterine fundus palpable 2 cm below the umbilicus

[1] Modified from Rosenthal & Poliquin, 2022

Poll question #5

How would you clinically stage Ana's syphilis infection?

A. Primary syphilis

B. Secondary syphilis

C. Early latent syphilis

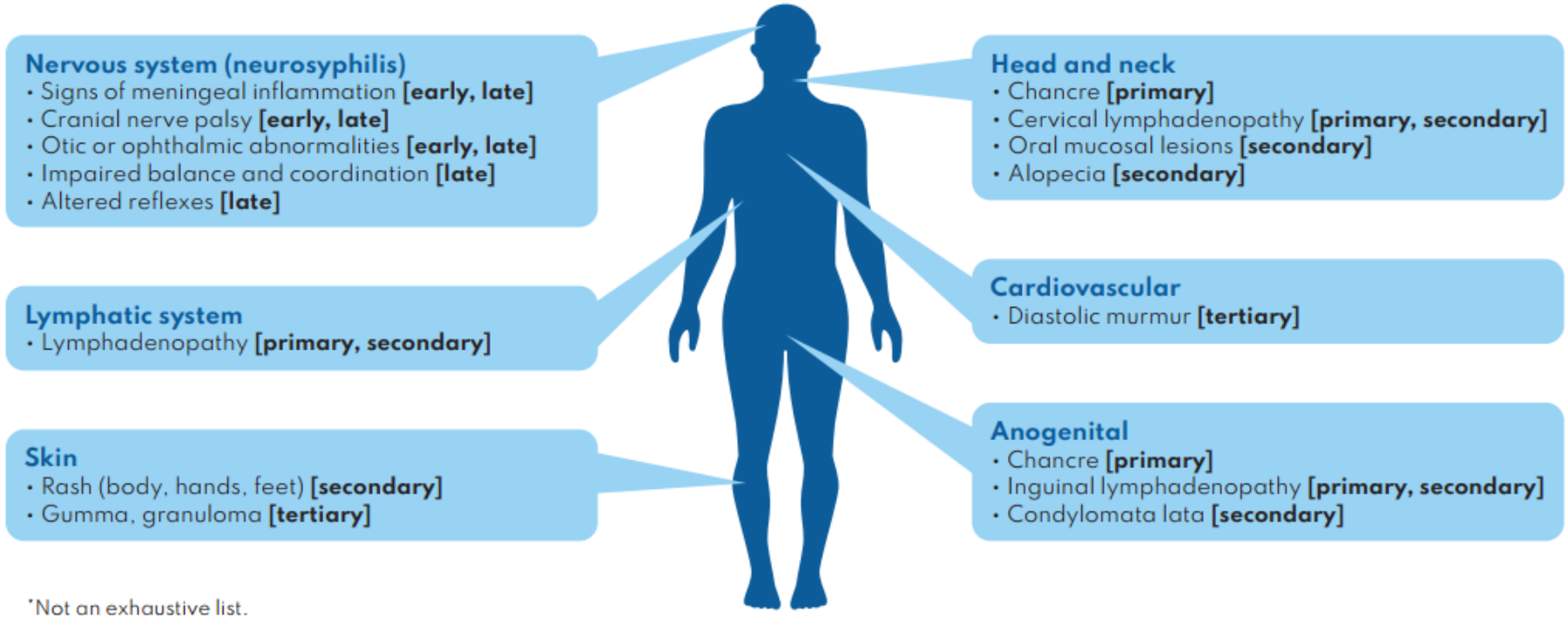
D. Late latent syphilis

E. Additional test results are required to clinically stage Ana's syphilis infection

Staging syphilis: History & physical exam findings

Staging a Syphilis Infection in Adolescents and Adults: Selected Physical Exam Findings According to Stage of Disease*

The clinical manifestations of syphilis are usually described according to stage of disease: primary, secondary, latent and tertiary syphilis. Early and late neurosyphilis can also occur.



*Not an exhaustive list.

(PHAC, 2024b; PHAC, 2024c)

Staging syphilis: History & physical exam findings

Staging a Syphilis Infection in Adults and Adolescents: Signs and Symptoms**

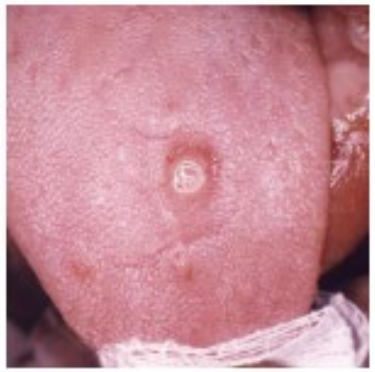
Primary Syphilis

Timing:

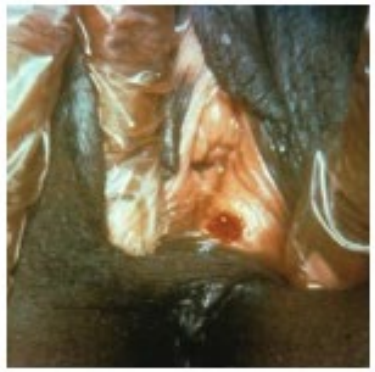
Usually occurs 3 weeks after infection, but can occur anywhere from 3 to 90 days post-infection.

Signs & symptoms:

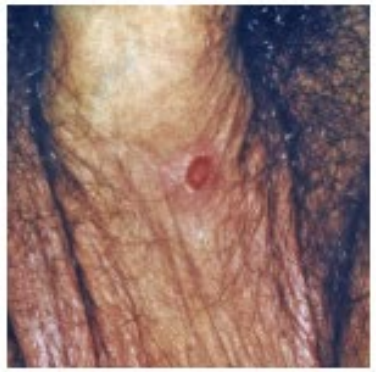
Painless lesion (chancre), regional lymphadenopathy.



(1.1) Oral chancre[1]



(1.2) Vaginal chancre[2]



(1.3) Penile chancre[3]

(1.4) Inguinal lymphadenopathy[4]

**See the Syphilis Guide for Health Professionals for more information.

(PHAC, 2024b; PHAC, 2024c)

Poll question #6

How is the word “titre” pronounced?

A “tee-ter”

B “tie-ter”

Syphilis laboratory and point-of-care tests

Standard laboratory tests			Point-of-care tests	
Conventional serological tests	Direct tests	Cerebrospinal fluid (CSF)	Syphilis POCT	Dual HIV/ syphilis POCT
Treponemal tests (TT) e.g., EIA, CMIA, TP-PA, FTA-ABS	NAAT e.g., PCR	CSF VDRL	TT e.g., MedMira Reveal™ Rapid TP Antibody test	Syphilis component is a TT e.g., bioLytical INSTI Multiplex HIV-1/2 Syphilis Ab test, MedMira Multiplo™ Rapid TP/HIV test
Non-treponemal tests (NTT) e.g., VDRL, RPR	Direct fluorescence		TT + NTT e.g., Chembio DPP® Syphilis Screen & Confirm Assay, MedMira Multiplo Complete Syphilis (TP/nTP) antibody test	

Acronyms:

Ab: Antibody
DPP: Dual-path platform
FTA-ABS: Fluorescent treponemal antibody absorption test
INNO-LIA: Innogenetics line immunoassay
nTP: Non-*Treponema pallidum*
NAAT: Nucleic acid amplification test
NTT: Non-treponemal test
RPR: Rapid plasma reagin
TP-PA: *T. pallidum* particle agglutination
CMIA: Chemiluminescent microparticle immunoassay
EIA: Enzyme immunoassay
HIV: Human immunodeficiency virus
MHA-TP: Microhemagglutination assay for *T. pallidum*
TP: *Treponema pallidum*
TT: Treponemal test
VDRL: Venereal disease research laboratory

Standard laboratory serological testing for syphilis

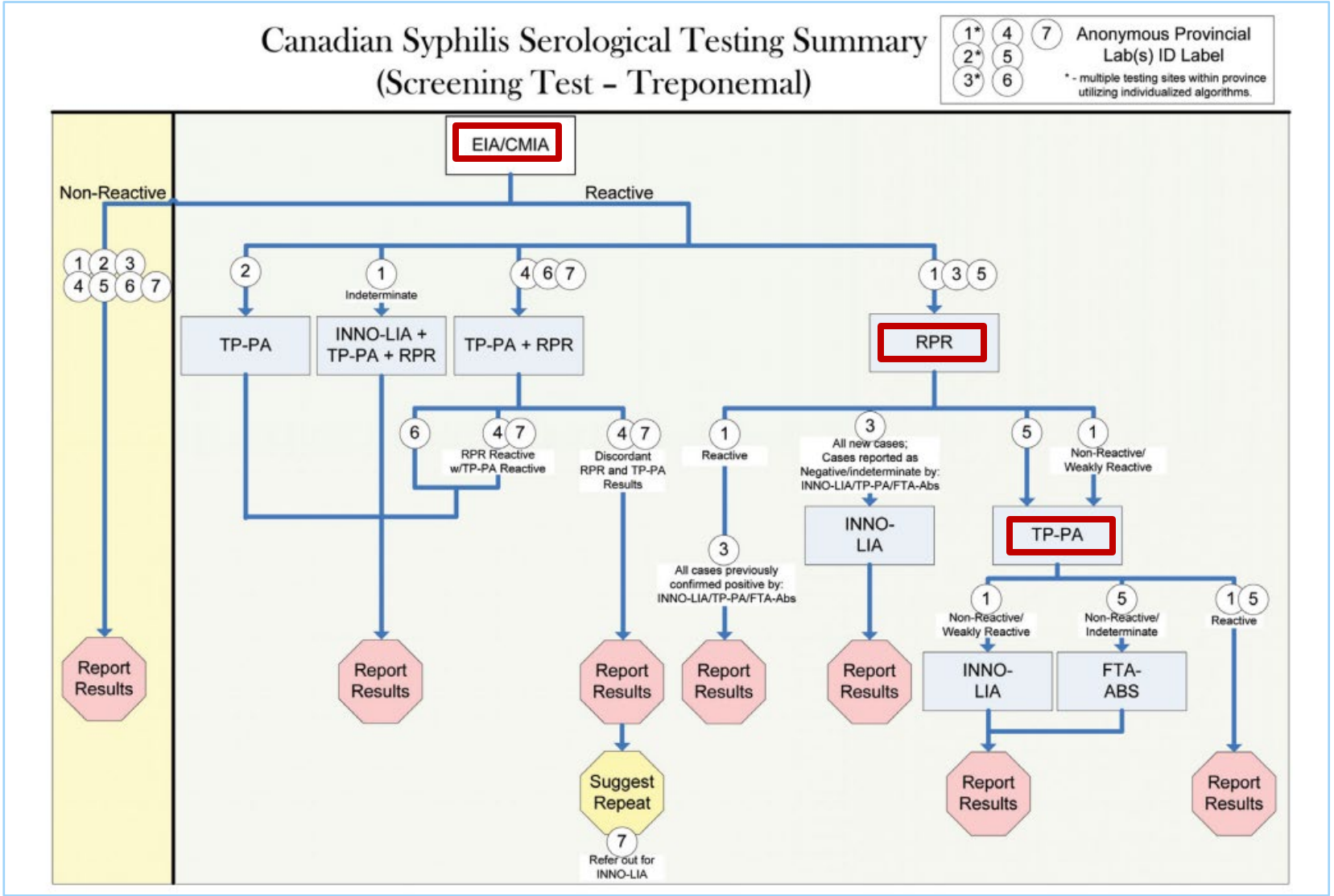
Screening

EIA / CMIA: Qualitative treponemal tests

Confirmatory

RPR: Quantitative non-treponemal test

TP-PA/ INNO-LIA/ FTA-ABS: Qualitative treponemal tests



(Levett et al., 2015, p.9A; Public Health Ontario, 2023)

Interpreting syphilis serologic tests

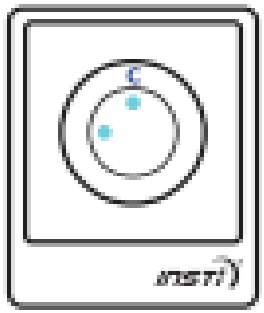
Screening TT (EIA/ CMIA)	Confirmatory NTT (RPR)	Confirmatory TT (TP-PA, FTA-ABS, INNO-LA)	Possible interpretation
Non-reactive	Not tested	Not tested	Not a case
Reactive	Non-reactive	Non-reactive	False positive Could also represent early syphilis, previously treated syphilis, or late latent syphilis infection
Reactive	Non-reactive	Reactive	Recent or prior syphilis infection
Reactive	Reactive 1:x*	Reactive	Recent or prior syphilis infection

Notes: RPR titre ≥ 1:8 is commonly used as a surrogate for infectious syphilis.
RPR can revert to non-reactive; this is less likely following re-infection.
An ≥ 4-fold increase in RPR (e.g., 1:1 → 1:4, 1:2 → 1:8) is concerning for re-infection or treatment failure.

(PHAC, 2024b)

Case 1: Ana[1]

Investigations:

Test	Source	Result	
bioLytical INSTI Multiplex HIV-1/2 Syphilis Ab test – syphilis component	Fingerstick	Reactive	
bioLytical INSTI Multiplex HIV-1/2 Syphilis Ab test – HIV component	Serum	Non-reactive	
Obstetrical ultrasound	N/A	Singleton pregnancy Estimated GA18+2 wks Nil abN	

(bioLytical Laboratories Inc., 2023)

[1] Modified from Rosenthal & Poliquin, 2022

Poll question #7

How would you treat Ana's syphilis infection?

A. Long-acting (LA) penicillin G 2.4 million IU IM x 1

B. Long-acting (LA) penicillin G 2.4 million IU IM qweekly x 2 doses

C. A or B, whichever is recommended by local experts

D. Doxycycline 100 mg po BID x 14 days

E. Defer treatment pending results of confirmatory laboratory tests

Treatment of syphilis in pregnancy

TREAT **Early diagnosis and treatment lead to better health outcomes**

Preferred treatment for syphilis in the absence of contraindications or allergies.

Primary, secondary, and early latent syphilis	Late latent and tertiary syphilis
Benzathine penicillin G-LA 2.4 million units IM x 1 dose	Benzathine penicillin G-LA 2.4 million units IM weekly x 3 doses

- Manage syphilis in pregnancy in consultation with an obstetric/maternal-fetal specialist. Some experts recommend 2 doses of benzathine penicillin G-LA 2.4 million units 1 week apart for primary, secondary and early latent syphilis in pregnancy, particularly in the third trimester.
- Refer individuals with neurosyphilis to a neurologist or infectious disease specialist.
- Inform patients about the Jarisch-Herxheimer reaction after treatment with penicillin.
- Consider treating sexual contacts of primary, secondary and early latent syphilis from the previous 90 days, especially if they may be lost to follow-up.
- Recommend to individuals and partners to abstain from sexual contact for 7 days after treatment.

(PHAC, 2024a)

The Jarisch-Herxheimer reaction

- Acute febrile reaction in the 24 hours following administration of penicillin for syphilis (most often secondary)
  - Fever, chills, rigors, myalgia, headache, bone pain, exacerbation of skin lesions

- In pregnancy, can be associated with fetal distress and preterm labour
  - 40-45% rates of J-H reaction in pregnancy have been reported; in a MB case series, rate was 1.7%
  - PHAC's **Syphilis Guide** suggests: If ultrasound is normal, can manage syphilis in pregnancy in outpatient settings and advise patients to seek medical attention for fever, contractions, or decreased fetal movement

(Dhaliwal et al., 2021; Ghanem, 2017; PHAC, 2023d)

Case 1: Ana[1]

Investigations:

Test	Source	Result
Treponema pallidum CMIA	Serum	Reactive
RPR	Serum	Reactive, 1:64
Treponema pallidum direct fluorescence*	Vulvar lesion	Detected

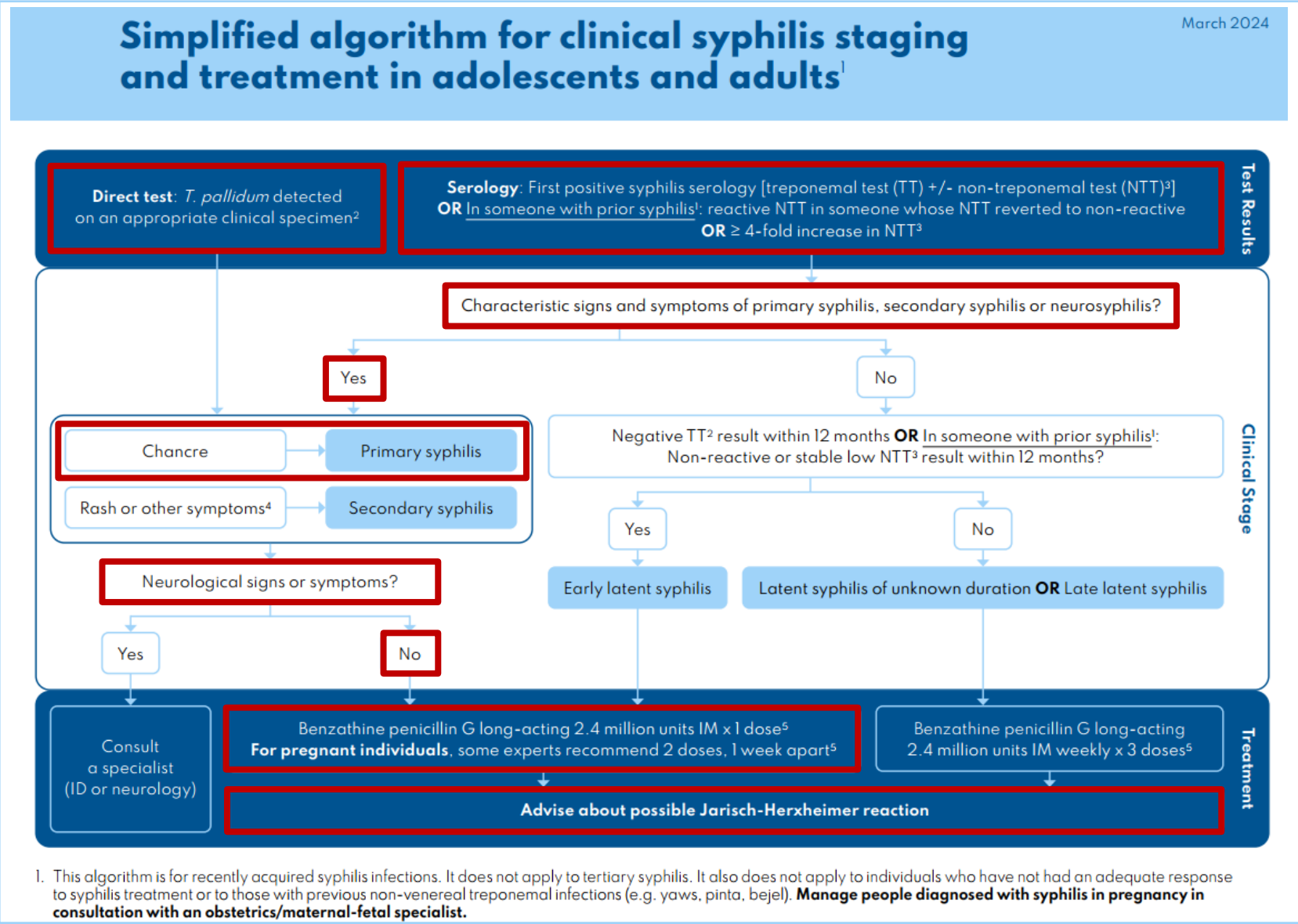
* Direct fluorescence is not reliable for oral or rectal lesions

Acronyms:

CMIA: Chemiluminescent microparticle immunoassay
RPR: Rapid plasma reagin

[1] Modified from Rosenthal & Poliquin, 2022

Simplified algorithm for clinical staging and treatment



Check out the full algorithm here:

Algorithm for staging and treating syphilis infection

Note: This algorithm will be posted to Canada.ca/syphilis in the coming months.

(PHAC, 2024c; PHAC, 2024d)

Syphilis follow-up

FOLLOW-UP **Monitor patients and notify contacts**

Confirm response to treatment with serologic testing. Notify, assess, and test contacts.

Stage	Follow-up serological testing	Trace back period
Primary, secondary, and early latent syphilis	At 3, 6, and 12 months **Pregnancy**: At 1, 3, 6, and 12 months (monthly if at risk of re-infection)	Primary: 3 months Secondary: 6 months Early latent: 1 year
Late latent and tertiary syphilis	At 12 and 24 months **Pregnancy**: At delivery, and at 12 and 24 months	Long-term sexual partner(s) and children as appropriate
Neurosyphilis	At 6, 12, and 24 months	Not applicable
Co-infection with HIV	At 3, 6, 12, 24 months, then yearly	Not applicable

(PHAC, 2024a)

Serologic response to treatment

Decline in non-treponemal test (NTT) titre after treatment is variable, and depends on:

- Stage of infection at the time of treatment
- NTT titre at treatment
- Prior treatment for syphilis

Syphilis stage	Adequate serologic response (NTT titre)	
	6 months after treatment	12 months after treatment
Primary syphilis	4-fold	8-fold
Secondary syphilis	8-fold	16-fold
Early latent syphilis	N/A	4-fold

(PHAC, 2024c)

Poll question #8

Ana's baseline RPR was 1:64. What follow-up titre(s) would indicate an adequate treatment response 6 months after treatment?

- **A** 1:8
- **B** 1:4
- **C** 1:16
- **D** 1:2
- **E** All of the above

Serologic response to treatment

- A 4-fold increase in NTT titre is concerning for treatment failure or re-infection

- Treatment failure in pregnancy is rate before 20 weeks' GA
- Treatment failure in pregnancy is associated with:
  - Sonographic signs of fetal syphilis;
  - Longer interval between infection and treatment;
  - Infection acquired in the third trimester; and
  - NTT titre ≥ 1:32

(PHAC, 2024c)

Syphilis screening, diagnosis and management in pregnancy

NAC-STBBI recommends screening for syphilis:

- In the first trimester or at the first prenatal visit
- In areas experiencing outbreaks and for people at ongoing risk, re-screen in the third trimester and at labour

Diagnosis, management, and follow-up:

- History, physical exam, and current and historical laboratory results support syphilis staging
- Treat syphilis in pregnancy in consultation with an obstetric or maternal-fetal specialist
  - There is no satisfactory alternative to penicillin for syphilis in pregnancy
- Follow non-treponemal titres to confirm that treatment has been effective
  - A ≥ 4-fold increase in titre is concerning for treatment failure or re-infection

03 CASE 2: Kris

Latent syphilis of unknown duration

Case 2: Kris

Patient information

- 25-year-old cisgender man

Reason for visit

- Presents to outpatient clinic for routine STBBI screening
- Last testing 15 months ago

Medical history

- Partners are cisgender men; engages in receptive and insertive anal sex
- Has not noticed any signs or symptoms of STBBI
- No known STBBI exposures
- Early latent syphilis 3 years ago (RPR declined to low stable titre of 1:1 following treatment; last serological result is from previous testing 15 months ago)
- Rectal chlamydia 2 years ago
- No medications
- No known drug allergies

Poll question #9

According to PHAC's STBBI: Guides for Health Professionals, how frequently should non-pregnant sexually active adolescents and adults with new or multiple sexual partners be screened for syphilis?

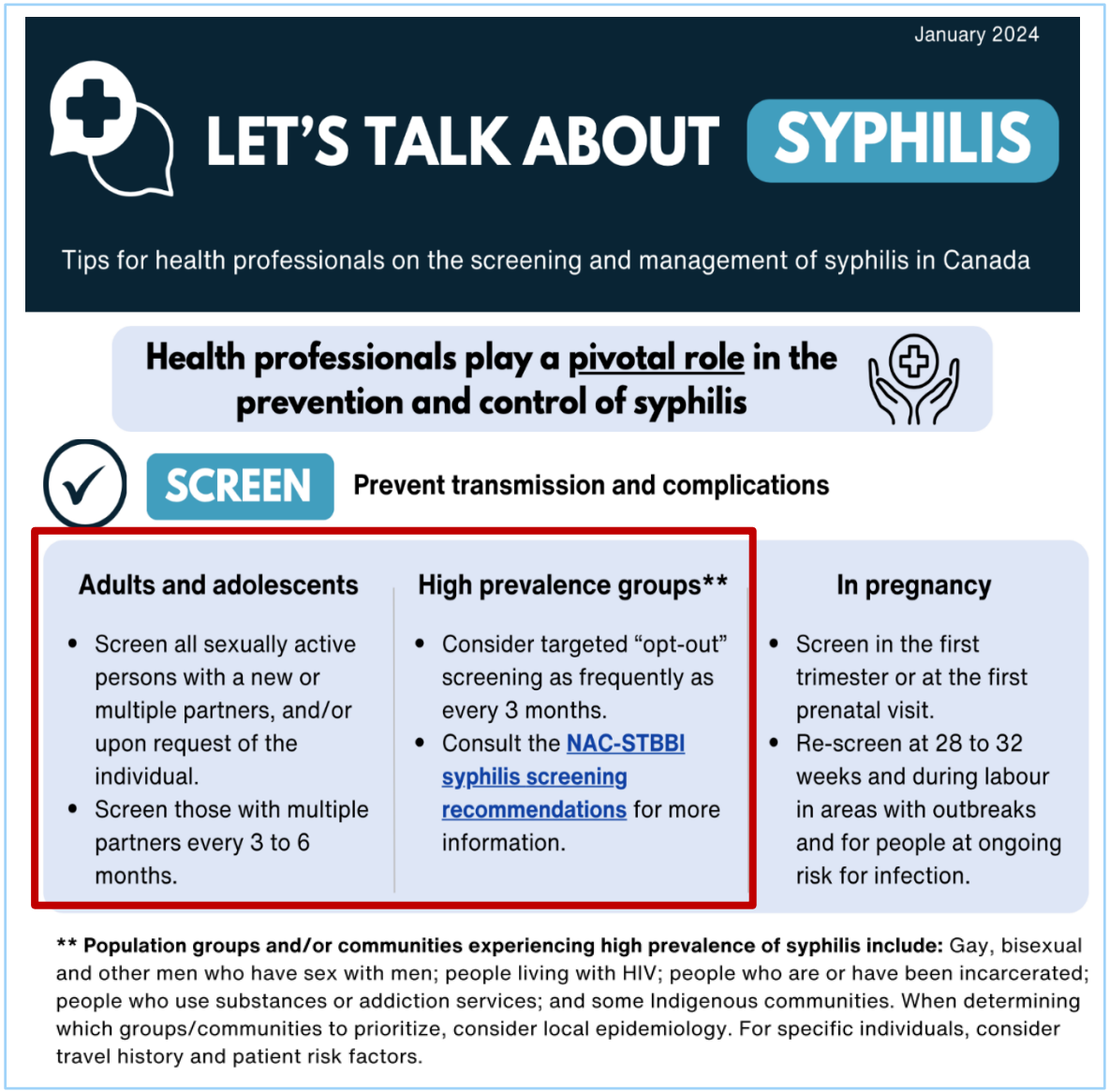
A. Every 3 - 6 months

B. Every 4 - 8 months

C. Every 12 months

D. Every 24 months

Syphilis screening for non-pregnant adolescents and adults



(PHAC, 2024a)

Case 2: Kris

Investigations:

Test	Source	Result
Treponema pallidum CMIA	Serum	Reactive
RPR	Serum	Reactive, 1:32
HIV Ab/Ag CMIA screen	Serum	Not detected
Neisseria gonorrhoeae NAAT	Urine	Not detected
Chlamydia trachomatis NAAT	Urine	Not detected
Neisseria gonorrhoeae NAAT	Throat swab	Not detected
Chlamydia trachomatis NAAT	Throat swab	Not detected
Neisseria gonorrhoeae NAAT	Rectal swab	Not detected
Chlamydia trachomatis NAAT	Rectal swab	Not detected

Acronyms: **CMIA**: Chemiluminescent microparticle immunoassay
NAAT: Nucleic acid amplification test
RPR: Rapid plasma reagin

Poll question #10

How would you clinically stage Kris's syphilis infection?

A. Previously treated syphilis

B. Primary syphilis

C. Secondary syphilis

D. Early latent syphilis

E. A clinical exam is needed to stage Kris's infection

Case 2: Kris

Reason for visit

- Recalled for a clinical staging assessment

Medical history

- Affirms that has not had any known exposures to syphilis
- Has not experienced any signs or symptoms of a syphilis infection

On examination

- Nil abnormal

(PHAC, 2024b; PHAC, 2024c)

Poll question #11

How would you clinically stage Kris's syphilis infection?

A. Previously treated syphilis

B. Primary syphilis

C. Secondary syphilis

D. Latent syphilis of unknown duration

E. Late latent syphilis

Staging syphilis: History & physical exam findings

Latent Syphilis

Timing:

Early latent syphilis is an asymptomatic infection of less than 1 year duration. It is considered infectious because of the 25% chance of relapse to the secondary stage.

Latent syphilis of unknown duration is an asymptomatic infection where the duration cannot be confirmed (i.e. no serologic testing within the prior 12 months).

Late latent syphilis is an asymptomatic infection of more than 1 year duration.

Signs & symptoms:

All latent syphilis infections are present without signs or symptoms.

Check out the full visual guide here:

Visual guide for staging syphilis infection

Note: This algorithm will be posted to Canada.ca/syphilis in the coming months.

(PHAC, 2024b; PHAC, 2024c)

Poll question #12

How would you treat Kris's syphilis infection?

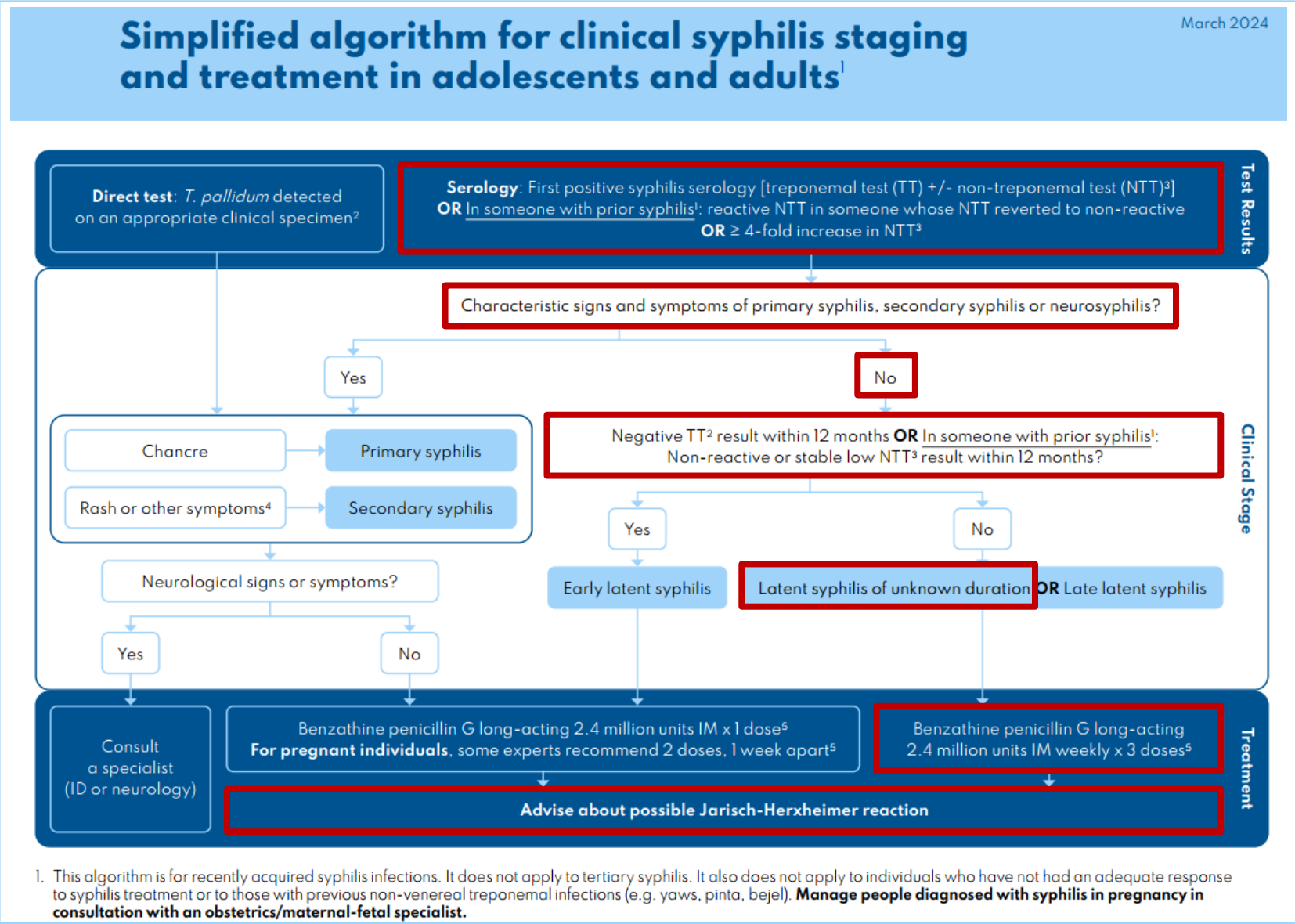
A. Long-acting (LA) penicillin G 2.4 million IU IM x 1

B. Long-acting (LA) penicillin G 2.4 million IU IM qweekly x 2 doses

C. Long-acting (LA) penicillin G 2.4 million IU IM qweekly x 3 doses

D. Doxycycline 100 mg po BID x 14 days

Simplified algorithm for clinical staging and treatment



Latent syphilis of unknown duration is generally treated as **late latent syphilis**

Check out the full algorithm here:

[Algorithm for staging and treating syphilis infection]

(PHAC, 2024c; PHAC, 2024d)

Recommended treatment of syphilis in non-pregnant adults

Recommended treatment of syphilis in non-pregnant adults

Stage	Preferred treatment	Alternative treatment for people with penicillin allergies
Primary, secondary and early latent syphilis	Benzathine penicillin G-LA 2.4 million units IM as a single dose [A-II] [2], [3], [4], [5], [6], [7].	• Doxycycline 100 mg PO BID for 14 days [B-II] [8], [9] • In exceptional circumstances and when close follow-up is assured: ◦ Ceftriaxone 1 g IV or IM daily for 10 days [B-II] [10]

Latent, late latent, cardiovascular syphilis and gumma	Benzathine penicillin G-LA 2.4 million units IM weekly for three (3) doses [AII] [11], [12]	• Consider penicillin desensitization
		  ◦ Doxycycline 100 mg PO BID for 28 days [B-II] [13]
		• In exceptional circumstances and when close follow-up is assured:
		  ◦ Ceftriaxone 1 g IV or IM daily for 10 days[C-III] [14]

All adults: Neurosyphilis	• Refer to a neurologist or infectious disease specialist	

(PHAC, 2024c)

Syphilis follow-up

FOLLOW-UP **Monitor patients and notify contacts**

Confirm response to treatment with serologic testing. Notify, assess, and test contacts.

Stage	Follow-up serological testing	Trace back period
Primary, secondary, and early latent syphilis	At 3, 6, and 12 months **Pregnancy**: At 1, 3, 6, and 12 months (monthly if at risk of re-infection)	Primary: 3 months Secondary: 6 months Early latent: 1 year
Late latent and tertiary syphilis	At 12 and 24 months **Pregnancy**: At delivery, and at 12 and 24 months	Long-term sexual partner(s) and children as appropriate
Neurosyphilis	At 6, 12, and 24 months	Not applicable
Co-infection with HIV	At 3, 6, 12, 24 months, then yearly	Not applicable

Follow-up testing and partner notification for latent syphilis of unknown duration generally follows recommendations for **early latent syphilis**

(PHAC, 2024a)

Case 2: Kris

Reason for visit

- Clinic nurse asks you to assess Kris when he returns for his second dose of LA penicillin G

Medical history

- After the first dose, Kris did experience transient myalgia, sweats and chills, and the appearance of a diffuse, red, rough, skin rash

On examination

- Erythematous maculopapular lesions over trunk and extremities, involving the palms and soles

Poll question #13

How would you clinically stage Kris's syphilis infection given this new information?

A. Primary syphilis

B. Secondary syphilis

C. Early latent syphilis

D. Latent syphilis of unknown duration

E. Late latent syphilis

Staging syphilis: History & physical exam findings

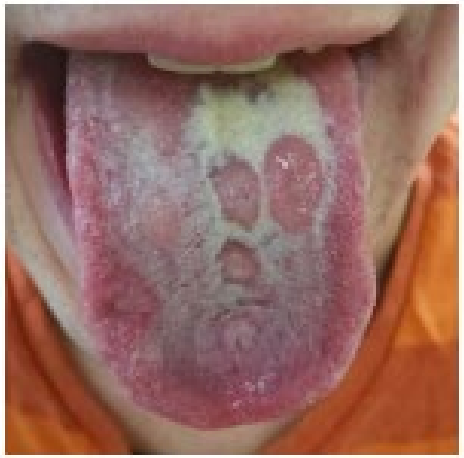
Secondary Syphilis

Timing:

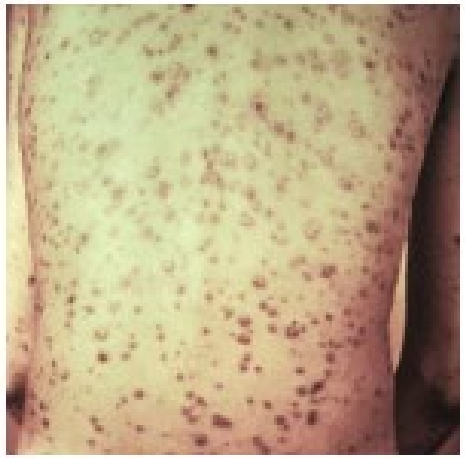
Usually occurs from 2 to 12 weeks after infection, but can occur up to 6 months post-infection.

Signs & symptoms:

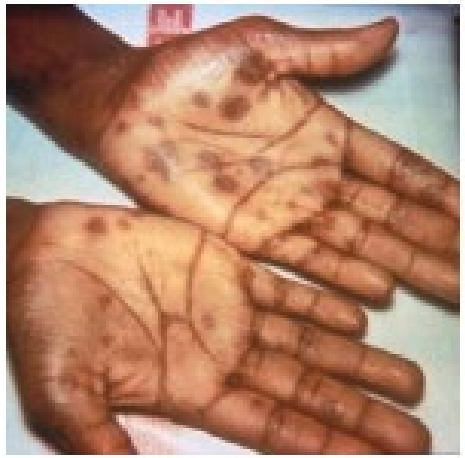
Rash, fever, malaise, mucosal lesions, condylomata lata, lymphadenopathy, patchy or diffuse alopecia.



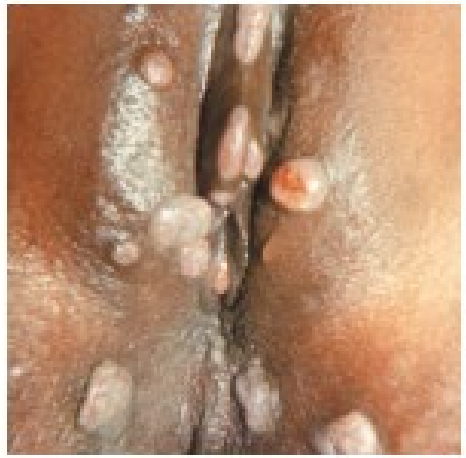
(2.1) Mucosal lesions on tongue[5]



(2.2) Secondary syphilis rash on body[6]



(2.3) Secondary syphilis palmar rash[7]



(2.4) Vaginal condylomata lata[8]

(PHAC, 2024b; PHAC, 2024c)

Reminder: Serologic response to treatment

Decline in non-treponemal test (NTT) titre after treatment is variable, and depends on:

- Stage of infection at the time of treatment
- NTT titre at treatment
- Prior treatment for syphilis

Syphilis stage	Adequate serologic response (NTT titre)	
	6 months after treatment	12 months after treatment
Primary syphilis	4-fold	8-fold
Secondary syphilis	8-fold	16-fold
Early latent syphilis	N/A	4-fold

(PHAC, 2024c)

Poll question #14

Kris's baseline RPR was 1:32. What follow-up titre(s) would indicate an adequate treatment response 6 months after treatment?

A. 1:8

B. 1:4

C. 1:16

D. 1:2

E. B and D are both correct

Syphilis screening, diagnosis and management for non-pregnant adolescents and adults

NAC-STBBI recommends screening for syphilis:

- All sexually active non-pregnant adolescents and adults with a new or multiple sexual partners every 3-to-6 months.
  - Targeted “opt-out” screening q3months should be considered when serving population groups/communities experiencing a high prevalence of syphilis.

Diagnosis, management, and follow-up:

- Syphilis laboratory results within the prior year enable staging an asymptomatic individual as early latent syphilis.
  - In the absence of historical lab results, an asymptomatic individual may be stated as ‘latent syphilis of unknown duration’.
- ‘Latent syphilis of unknown duration’ is generally treated as late latent syphilis and contact management is as per early latent syphilis.

Links to key resources

Syphilis factsheet

- Let's talk about syphilis: Tips for health professionals on the screening and management of syphilis in Canada

Google Drive links to syphilis resources

- Visual guide for staging syphilis infection
- Algorithm for staging and treating syphilis infection
- Strategies for implementing a person-centered approach to sexual health

Note: These resources will be posted to Canada.ca/syphilis in the coming months.

Thank you!

Questions?

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