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Syphilis: controlling an old disease with modern technologies.

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Disclosure / disclaimer:

I have no conflicts of interest to declare.

Views expressed in this presentation are my own and do not reflect the view of NMLB nor PHAC.

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○ **The Learning Objectives are:**

- Explain laboratory diagnostic methods for syphilis
- Describe PHAC's Five-Year Action plan on STBBI with emphasis on syphilis and National Microbiology Laboratory Branch's response to the current increase in infection rates.
- Recognize newer diagnostic methods and appreciate the challenges in syphilis diagnosis



Presentation content

- Causative agent and characteristics
- Origin / History of syphilis infection
- Laboratory diagnosis of syphilis and surveillance case definition
- Recent epidemiology of infectious syphilis in Canada
- Pan Canadian framework on STBBI
- Government of Canada's five-year action plan on STBBI
- Newer diagnostic methods
- Challenges in the control of syphilis
- Conclusion
- Acknowledgements

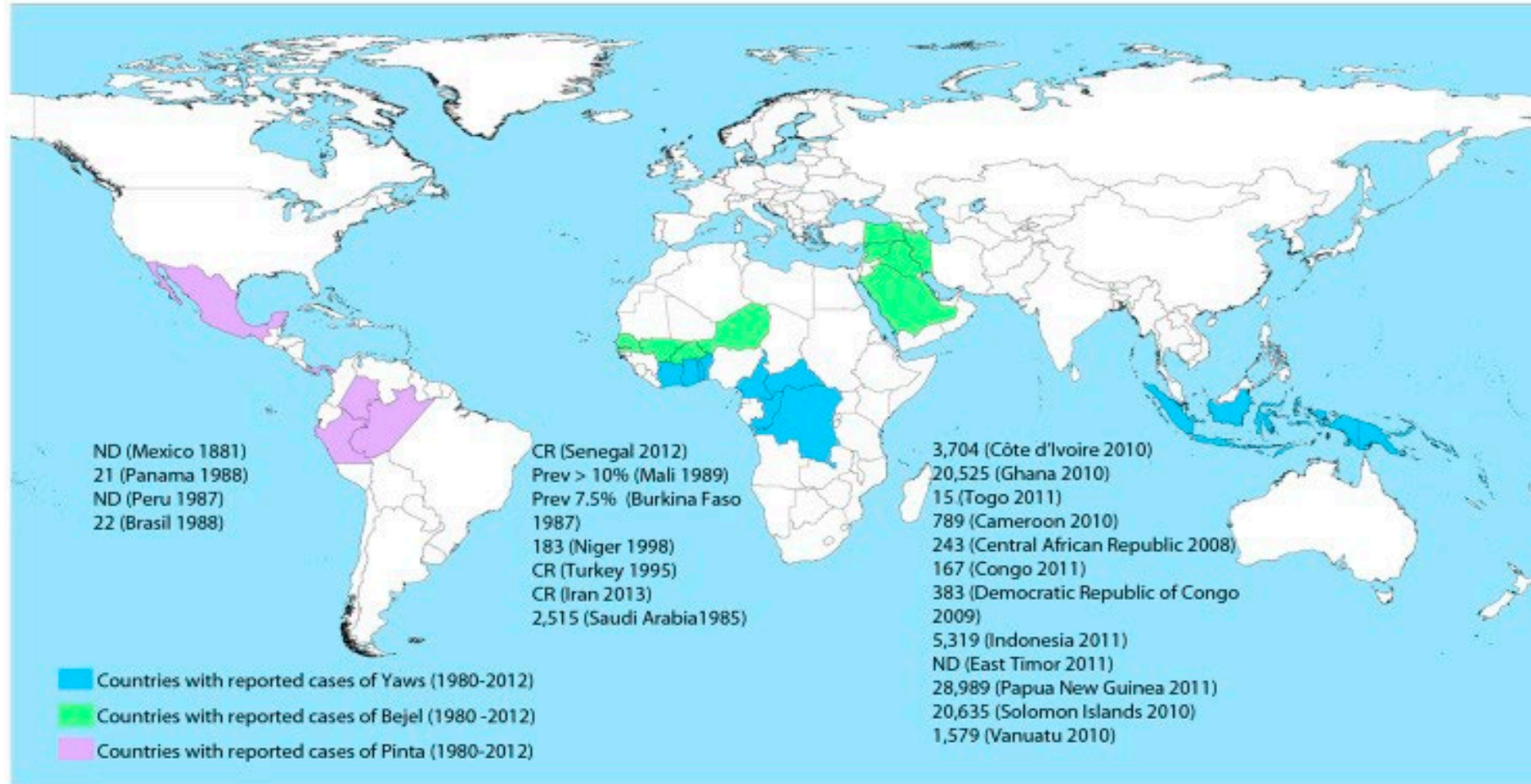




Syphilis: the causative agent and its characteristics

- Syphilis is caused by *Treponema pallidum* subspecies *pallidum*.
- Two other subspecies of *T. pallidum*, subspecies *endemicum* which causes non-venereal syphilis or bejel; and subspecies *pertenue* which causes yaws.
- *T. carateum* causes pinta.
- Syphilis and non-venereal treponemal diseases.
- Only syphilis is transmitted sexually and also, vertically from infected mothers to babies as well as via blood.
- Non-venereal treponemal diseases are usually transmitted by non-sexual direct contact.
- Bejel or endemic syphilis occurs in dry regions of eastern Mediterranean and Saharan West Africa.
- Yaws occurs in humid equatorial countries.
- Pinta occurs in Mexico, Central America, and South America.





Source: Oriol Mitja, David S`majš, Quique Bassat. PLoS Neglected Tropical Diseases, 2013; Volume 7, issue 10: pp. e2283.





Characteristics of causative agent continues

- Spiral organism with unique motility: Rotation of the flagella in the periplasm causes the entire cell body to rotate and/or undulate.
- Invasive bacteria
- Immune-evasiveness: described as a “Stealth pathogen”*
- Non-culturable
- Antigenically very similar among the pathogenic treponemes

* *Treponema pallidum*, the stealth pathogen, doth change, but how?

JD Radolf & DC Desrosiers. Molecular Microbiology 2009; 72 (5): pp. 1081-1086





Brief history of syphilis infection

Origin of syphilis

- Pre-Columbian hypothesis: Pinta existed in Africa-Asia around 15,000 BC. The causative agent of yaws arose from *T. carateum* around 10,000 BC and spread around the world (except the New World). The agent of endemic syphilis arose from yaws around 7,000 BC, and around 3,000 BC, the causative agent of venereal syphilis emerged and Columbus brought it to the New World.
- Columbian hypothesis, Christopher Columbus' seamen brought it to Europe after the discovery of the New World. This timing correlates with the first reported outbreaks in Europe during the war of Naples in 1495.





Origin of syphilis continues

- Unitarian hypothesis: both syphilis and non-venereal treponemal diseases are variants of the same infection, and the clinical differences of these diseases are results of geography, climate conditions, cultural differences. Or the original treponema adapted to different environment and host customs to become agents causing syphilis, bejel, yaws and pinta.

Sources:

- History of syphilis. Clin Infect Dis 2005; **40**: pp. 1454-1465.
- Brief history of syphilis. J Med Life 2014; **15**: 4-10.
- Revisiting the Great Imitator: the origin and history of syphilis. American Society for Microbiology article June 17, 2019.





Laboratory diagnosis of syphilis

Direct detection

- Nucleic acid amplification test (NAAT)
- Immuno-histochemistry
- Specialized staining & microscopy in histo-pathology
- by microscopy, dark field or phase contrast microscope
- Direct fluorescent antibody test for *Treponema pallidum* or DFA-TP
- Rabbit infectivity test (obsolete)

Serology

Treponemal versus non-treponemal tests

Examples of treponemal tests:

EIA, CIA, TP-PA, FTA-ABS, syphilis Inno LIA

Examples of non-treponemal tests:

RPR, VDRL





Characteristics of serological tests

- Treponemal tests (TT) positivity may persist for very long time
- Non-treponemal tests: titers may decrease with treatment and hence following titers of non-treponemal test may be used to monitor response to treatment.
- A positive treponemal test alone can not be used to diagnose an active syphilis infection.
- A positive result in the treponemal test is required to confirm a true positive Non-TT.
- In the absence of other information, a positive result in both TT and Non-TT may still indicate a treated past infection esp. with low titer Non-TT result.
- Early in the infection, serological tests may be negative.
- Both syphilis and non-venereal treponemal infections can induce the same positive serological response.





Laboratory diagnosis related to case definitions

- A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance; it is not intended to be used by health care providers for making a clinical diagnosis.
- US CDC's National Notifiable Disease Surveillance System has case definitions for the following syphilis subtypes:
 - Syphilis, primary
 - Syphilis, secondary
 - Syphilis, early non-primary non-secondary
 - Syphilis, unknown duration or late
 - Syphilis, congenital
 - Syphilitic stillbirth

Source: US Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System: Syphilis (*Treponema pallidum*) 2018 Case Definition.

<https://ndc.services.cdc.gov/case-definitions/syphilis-2018/>

(last reviewed April 16, 2021)





Confirmed primary syphilis case:

A case that meets the clinical description of primary syphilis [which is a stage of infection with *T. pallidum* characterized by one or more ulcerative lesions (e.g. chancre), which might differ considerably in clinical appearance] and **the confirmatory laboratory criteria** [demonstration by dark field microscopy in a clinical specimen that was not obtained from the oropharynx and is not potentially contaminated by stool; or demonstration of *T. pallidum* by NAAT or equivalent molecular methods in any clinical specimen].





Probable primary syphilis case:

A case that meets the clinical description of primary syphilis and the supportive laboratory criteria.

Supportive laboratory criteria for diagnosis

- A reactive non-treponemal serologic test (such as VRDL or RPR)
- OR
- A reactive treponemal serologic test (TPPA, EIA, CIA).

Important message here: the use of direct detection method, especially nucleic acid amplification tests





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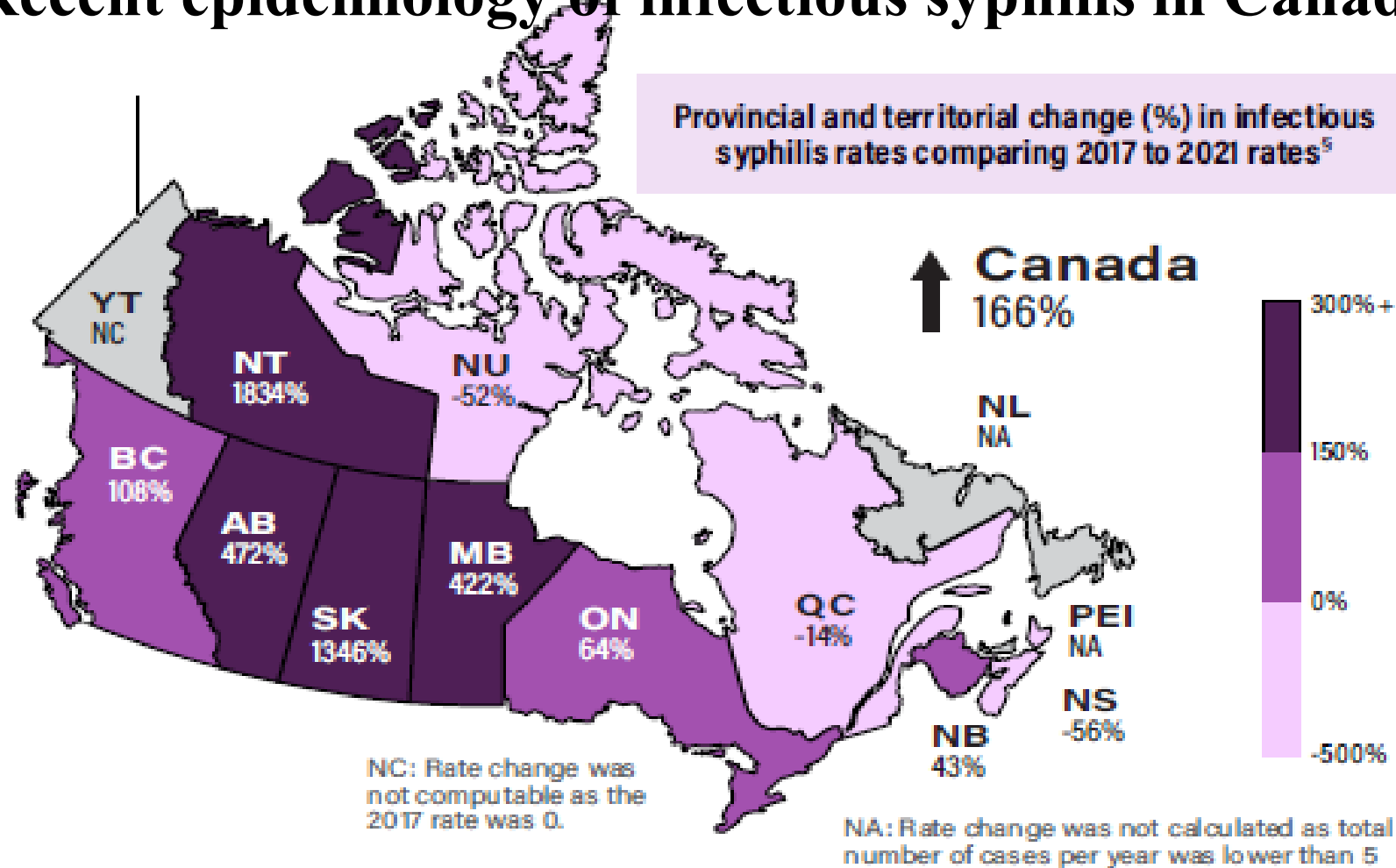
Canadian Case definition for syphilis

<https://www.canada.ca/en/public-health/services/diseases/syphilis/health-professionals/national-case-definition.html>





Recent epidemiology of infectious syphilis in Canada.

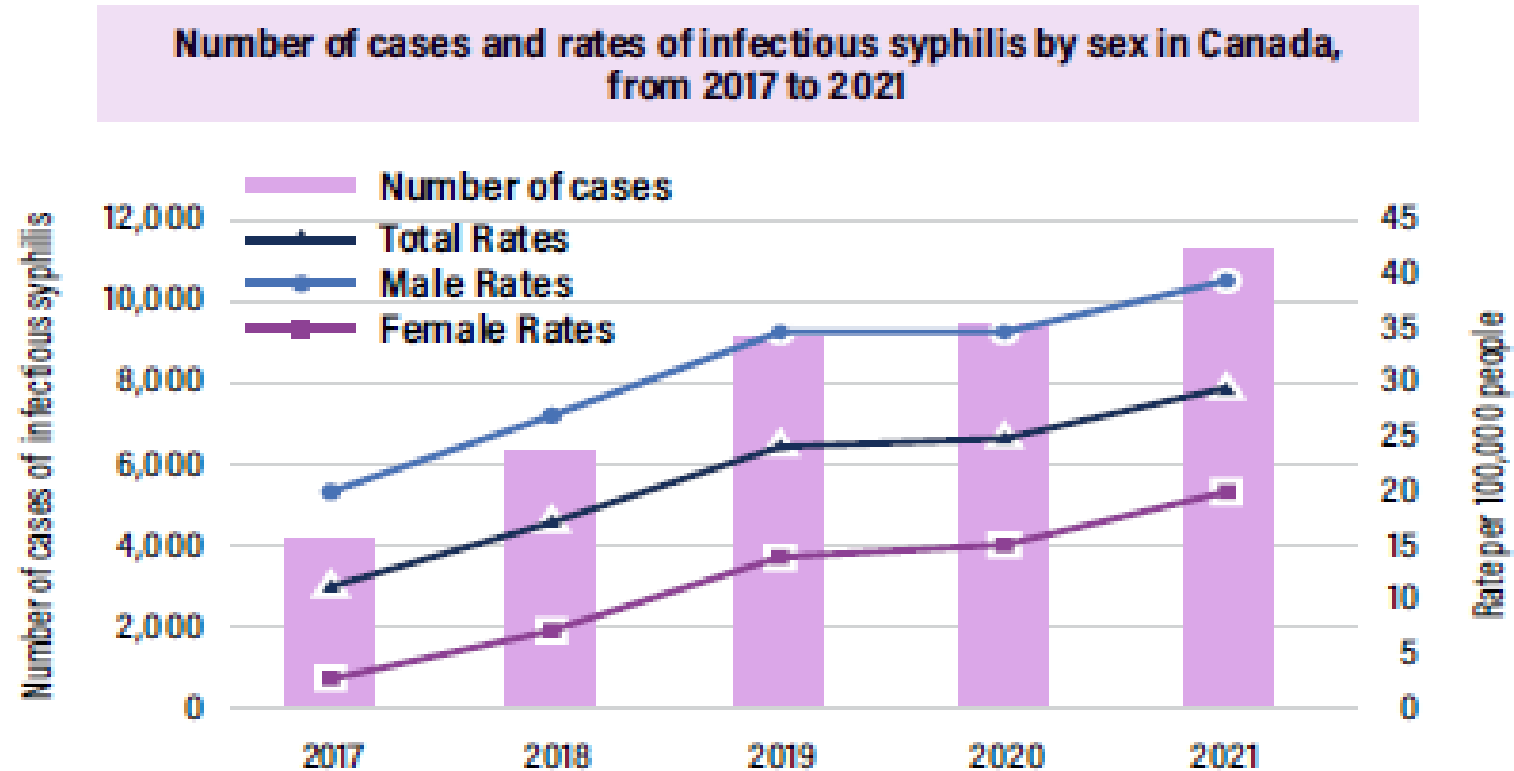


Source: STBBI Surveillance Division, PHAC. Published in 2022 CDR vol. 48(11/12): pp. 587





Recent epidemiology of infectious syphilis in Canada, continues



Source: STBBI Surveillance Division, PHAC. Published in 2022 CCDR vol. 48(11/12): pp. 587





Recent epidemiology of infectious syphilis in Canada, continues



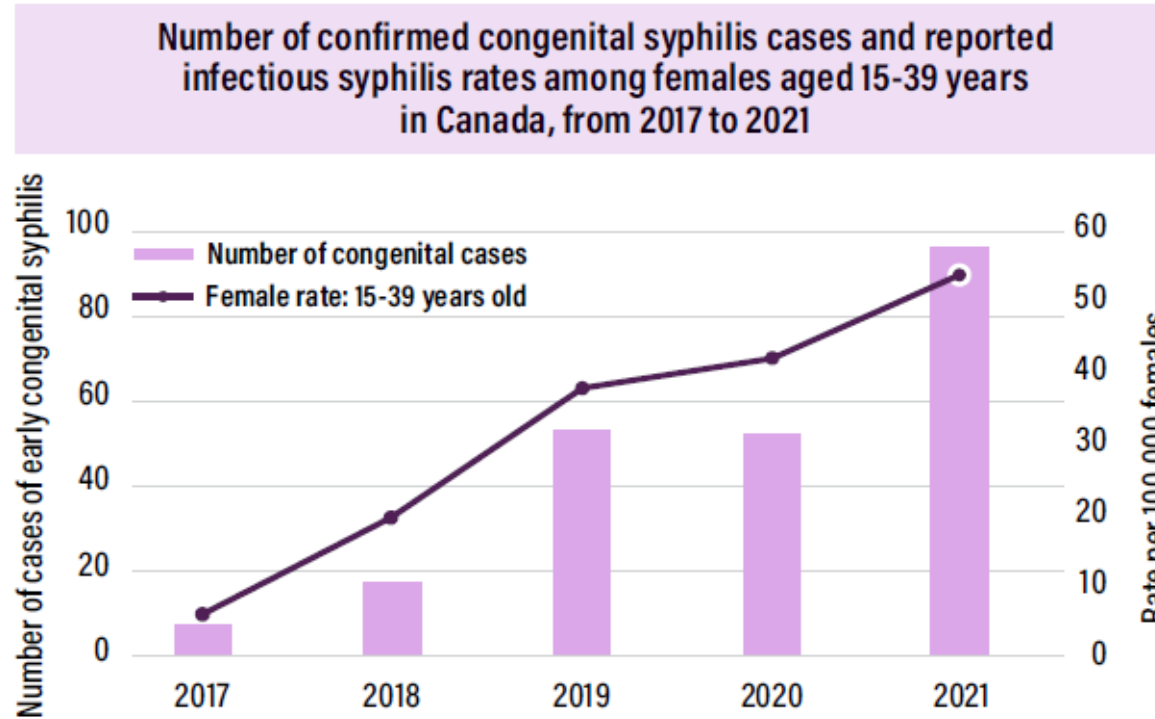
There were

96 CASES

of confirmed early congenital
syphilis[†] in 2021 compared to only
7 cases in 2017. An increase of 1271%.

Source: STBBI Surveillance Division, PHAC. Published in 2022 CCDR vol. 48(11/12): pp. 587





Source: Canada Communicable Disease Report 2022; **48** (11/12): 587





Global epidemiology as reported by World Health Organization (WHO)

- More than 1 million sexually transmitted infections (STIs) are acquired every day worldwide, the majority of which are asymptomatic
- Almost 1 million pregnant women were estimated to be infected with syphilis in 2016, resulting in over 350 000 adverse birth outcomes

Source: World Health Organization on Sexually Transmitted Infections, 10 July 2023

<https://www.who.int/publications/i/item/9789240053779>





WHO Response:

Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030.

Source:

<https://www.who.int/publications/i/item/9789240053779>

Goals and target for syphilis:

- Lower the number of new cases of syphilis among people 15–49 years old to 0.71 million per year by 2030.
- Lower congenital syphilis cases per 100,000 live births per year to less than 50 by 2030.





Pan-Canadian framework on STBBI

- Canada has endorsed the WHO Global health sector strategies on STBBI, the United Nations Sustainable Development Goals, and the Joint United Nations Programme on HIV/ AIDS (UNAIDS).
- These programs have a common goal of elimination of STBBI as a public health concern by 2030.
- To achieve this, the PHAC has developed a Pan-Canadian framework on STBBI, which has been endorsed by federal, provincial and territorial ministers of health.

Source: PHAC's Centre for Communicable Diseases and Infection Control; Summary of framework published in Canada Communicable Disease Report 2018; vol. 44 (7/8): pp. 179-181.





Pan-Canadian framework on STBBI

Goals:

- Reduce the incidence of STBBI in Canada
- Improve access to testing, treatment, and ongoing care and support
- Reduce stigma and discrimination that create vulnerabilities to STBBI





CORE PILLARS





Government of Canada's five-year action plan on STBBI

The GoC plan shares the strategic goals of the Pan-Canadian framework, which are

- Reduce the incidence of STBBI in Canada
- Improve access to testing, treatment, care and support
- Reduce the stigma and discrimination that creates vulnerabilities to STBBI

Source: C. Jackson, G. Tremblay on behalf of the Government of Canada STBBI Action Plan Steering Committee; published in Canada Communicable Disease Report 2019; vol. 45 (12): pp. 323-326.





GoC Five-year action plan on STBBI

Text box: Federal departments involved in the Government of Canada Five-Year Action Plan on Sexually Transmitted and Blood-Borne Infections:

- Public Health Agency of Canada
- Canadian Institutes of Health Research
- Correctional Service Canada
- Department of Justice
- Department of National Defence
- Department of Women and Gender Equality
- Health Canada
- Immigration, Refugees and Citizenship Canada
- Indigenous Services Canada
- LGBTQ2 Secretariat of the Privy Council Office

Source: Canada Communicable Disease Report 2019; vol. 45(12): pp. 323-326





NMLB contribution towards GoC Five-year Action

Plan: Newer diagnostic methods

- To improve access to testing, NMLB is working towards
 - a) Evaluating syphilis Point-of-Care Testing (POCT) --- by
 - i) Evaluating commercial POCT kits in the laboratory setting and
 - ii) Field evaluation which is done with Research Ethics Board (REB) approvals locally and at the federal level, as well as done under the approval of Health Canada Medical Device Directorate Investigational Testing Authority.
 - b) NMLB is working with provincial and territorial public health to develop CPHLN guidelines for the laboratory diagnosis of syphilis, including the use of POCT.





Landscape of Syphilis POCTs

- Currently available syphilis POCTs detect antibodies to the causative pathogen
- One category of product detects antibodies to *T. pallidum*
- Another category is multiplexed to detect antibodies to both *T. pallidum* and HIV-1/2
- Those that detects antibodies to *T. pallidum* can be further divided into (a) detect antibodies to treponemal antigen; and (b) detect antibodies to both treponemal and non-treponemal antigens
- In the WHO document “The diagnostic landscape for sexually transmitted infections”, described a total of 19 rapid diagnostic tests for syphilis with most having obtained either CE-IVD, or FDA, or WHO prequalification approval.

Source: The diagnostics landscape for sexually transmitted infections. WHO 2023. ISBN 978-92-4-007712-6 (electronic version).





Syphilis POCTs continues

- Eleven of the 19 POCTs are for detection of syphilis infection,
- seven are for detection of HIV and syphilis infection, and
- only one that detects syphilis infection based on measurement of antibodies to both treponemal and non-treponemal antigens
- However, in Canada, as of end of July 2023, Health Canada has only approved the **use** of one POCT that detects HIV and syphilis infection (INSTI multiplex HIV-1, HIV-2, and Syphilis Antibody Test] **by health care professionals**
- This is a single use rapid test that gives results in 60 seconds for detection of IgG and IgM antibodies to HIV-1, HIV-2, *and T. pallidum* in whole blood (obtained by finger prick or venipuncture), serum or plasma.
- The result is read visually and does not require any specialized reader.





Ideal characteristics of a POCT

- Should meet the **ASSURED** criteria introduced by the World Health Organization
- **A**ffordable, **S**ensitive, **S**pecific, **U**ser-friendly, **R**apid and **R**obust, **E**quipment free, and **D**eliverable to end-users
- as of 2023, no syphilis POCT has met all these criteria

Source:

Peeling RW, Holmes KK, Mabey D, Ronald A. Rapid tests for sexually transmitted infections (STIs): the way forward. *Sex Transm Infect* 2006; 82 (Suppl 5): v1-6.

World Health Organization. Point-of-care tests for sexually transmitted infections, target product profiles. World Health Organization 2023. ISBN 978-92-4-007710-2 (electronic version).





Other NMLB contributions towards GoC five-year action plan on STBBI

- Developing innovative diagnostic testing, including
 - a) Working with Dr. Venkata Duvvuri of PHO Lab to mine the genomes of *T. pallidum* to identify newer diagnostic markers
 - b) In collaboration with the National Research Council of Canada to develop rapid antigen detection test. NRC has a wide network of industrial partners through its Industry Research Assistance Program (IRIP) [<https://nrc.canada.ca/en/support-technology-innovation>] and its own Medical Device Research Centre.
 - c) Dr. John Kim's of NMLB has done work on dried blood spot.
- Working with Dr. Tom Braukmann of PHO Lab and other NMLB scientists and provincial public health laboratory partners to develop metagenomics methods and pipelines to provide molecular typing and AMR prediction.





Other NMLB contributions continues

- Dr. Paul Sandstrom and his STBBI team at the NMLB is also doing outreach and engagement activities with Indigenous populations to enable the environment for testing, prevention, treatment and care, as well as ongoing care and support.





Challenges in the control of syphilis

- The “Great Imitator”
- Lack of a vaccine for prevention
- Lack of rapid diagnostic tools that can identify infection and offer treatment at the same time.
- Limited choice of antibiotics for treatment





Challenges and solutions to implementation of syphilis POCT

- NMLB is working with its Canadian Public Health Laboratory Network (CPHLN) partners on how to capture POCT results once this is rolled out.
- NMLB is preparing for proficiency programs for control of test kits as well as to control quality performance by operators performing POCT.
- If POCT is deployed in a non-clinical setting, how would treatment be administered esp. in view of the current guideline for treatment of primary and secondary syphilis is parenteral long-acting penicillin.
- An oral antibiotic doxycycline has been proposed as a prophylactic agent for bacterial STI.
- **Source:** Doxycycline Prophylaxis for Bacterial Sexually Transmitted Infections. *Clinical Infectious Diseases* 2020; **70** (6): pp. 1247-1253.





Doxycycline prophylaxis

- Doxy PrEP, pre-exposure prophylaxis
 - Doxy PEP, postexposure prophylaxis
-
- Multi-centre clinical trials on use of doxycycline prophylaxis are happening, including in Canada.
 - PHAC is also following the results and examining the pros and cons for this approach in the control of bacterial STIs, including syphilis.
 - Whether doxycycline can be used for treatment of early syphilis when cases are identified by POCTs remains to be determined.





Conclusion

- Increase in syphilis infection is unprecedented involving both genders and leading to record number of congenital syphilis cases.
- Traditional way of lab diagnosis may not be adequate to identify, treat, and control the current level of transmission of syphilis.
- Newer technologies may be required:
 - POCT for detection of antibodies that can identify infectious syphilis.
 - POCT for detection of antigen
 - Preventive vaccines
 - Newer treatment options





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Thank you!

Questions?

