



Congenital syphilis



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Background

Syphilis is the third most common sexually transmitted bacterial infection in Canada, with a dramatic and rapid increase in confirmed cases over recent years, on top of a steady increase over the last decade (1,2). Although the majority of these cases are among men, cases among young women are of public health importance due to the potential for vertical transmission to the fetus during pregnancy. Vertical transmission can occur at any stage of pregnancy and can vary by the stage of illness in the mother, but it is estimated that between 60 to 100% of infants born to untreated mothers with primary or secondary stage infections will become infected (3). Many infants with congenital syphilis are asymptomatic at birth and, in situations where prenatal care is limited or syphilis testing was not done in pregnancy, the infection may go undiagnosed. This difficulty identifying affected infants is a major barrier to initiating

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treatment with penicillin, which is ubiquitous and can prevent late manifestations of congenital syphilis, if given early.

Paralleling the increase in syphilis among Canadian adults, the Public Health Agency of Canada has detected an increase in the incidence of congenital syphilis. In the decade prior to 2005, approximately two cases per year of congenital syphilis were reported nationally. From 2005 to 2017, an average of five cases per year was reported (1,4). In 2018, 17 cases of congenital syphilis were reported nationally, the highest incidence in 25 years. In Manitoba alone, over 26 confirmed cases of congenital syphilis were reported from 2015 to 2019 inclusive (5). Additionally, over 80 syphilis-exposed infants were reported in the first nine months of 2019 alone (5).

In those who survive the prenatal period, congenital syphilis infection impacts multiple organ systems over a lifetime. In-utero manifestations of congenital infection include stillbirth, hydrops fetalis, and preterm birth. Neonatal manifestations, when present, include hepatosplenomegaly, lymphadenopathy, rash, copious secretions (“snuffles”), osteochondritis, hemolytic anemia, thrombocytopenia, and pneumonia (3). Late manifestations, which are preventable by early treatment, include sensory deficits, musculoskeletal deformities, and developmental impairment (3).

The disease can prove challenging to diagnose at birth, as about 60% of infected neonates are asymptomatic (6). Moreover, there is confusion among clinicians regarding the interpretation of maternal and infant syphilis serologies, a problem compounded by both false negatives and false positives in late pregnancy. Taken together, these two challenges likely result in under-recognition of cases of congenital syphilis and it is likely that cases of “probable” congenital syphilis are not included in incidence figures reported by the Public Health Agency of Canada.

All provinces and territories voluntarily submit limited data on nationally notifiable diseases to the Canadian Notifiable Disease Surveillance System (4). While congenital syphilis is nationally reportable, case-level data on the diagnosis, treatment, and ongoing management of congenital syphilis in Canada is lacking. The American Academy of Pediatrics’ 2018 *Red Book* recommends that neonates born to women testing positive for syphilis undergo hematologic, cerebrospinal fluid, and radiographic investigations (testing depends on case specifics); however, it is unclear to what degree these investigations are completed in each case (3). The appropriateness, completeness of, and results from this work up are subsequently used to diagnose congenital syphilis, and to determine the duration of antibiotic therapy (either a single dose of intramuscular benzathine penicillin G or 10 days of intravenous aqueous penicillin G). Many affected neonates are unknowingly treated for inadequately short durations, or the diagnosis is missed all together.

Methods

Through the standard methods of the Canadian Paediatric Surveillance Program (CPSP), approximately 2,800 paediatricians and paediatric subspecialists will be actively surveyed on a monthly basis to determine whether they have seen a new confirmed or suspected case of congenital syphilis in the preceding month. Respondents who have seen a case will receive a detailed questionnaire to complete in order to gather case-level information on demographics, diagnostic evaluation, treatment and follow up, and referrals.



Congenital syphilis (continued)

The study investigators include representatives from a variety of subspecialties such as infectious diseases, public health, medical microbiology, and general paediatrics from across the country. The investigators will use their national connections to promote reporting of cases in subspecialty circles, at their institutions, and through regional platforms.



Case definition

Report any neonate, infant, or child <4 years old with a new diagnosis of confirmed or probable congenital syphilis in the last month.

Confirmed congenital syphilis (requires one of the following)

1. Identification of *Treponema pallidum* in the infant/child's specimen by polymerase chain reaction (PCR) or fluorescent antibody examination
2. Reactive serology from venous blood in an infant that is four-fold greater than the maternal serology collected near the time of birth
3. Reactive serology from venous blood in an infant that persists beyond their second birthday

Probable congenital syphilis

1. Infant born to a mother who had untreated or inadequately treated syphilis at delivery, regardless of findings in the infant

OR BOTH OF THE FOLLOWING:

2. An infant or child with a reactive treponemal test result
3. One of the following additional criteria:
 - a. Clinical signs of congenital syphilis on physical examination
 - b. Evidence of congenital syphilis on radiographs of long bones
 - c. Abnormal cerebrospinal fluid cell count or protein without other cause
 - d. Reactive treponemal immunoglobulin M (IgM) (19S-IgM antibody test or IgM enzyme-linked immunosorbent assay)

Objectives

- 1) Describe the minimum incidence and national distribution of new cases of confirmed or probable congenital syphilis
- 2) Identify common risk factors of mothers with affected children and the treatment they received during pregnancy
- 3) Describe diagnostic testing, management, and complications of neonates, infants and children with confirmed or probable congenital syphilis

Duration

June 2021 to May 2023

Expected number of cases

Congenital syphilis is a reportable condition with 17 confirmed cases nationally in 2018 according to the Public Health Agency of Canada. It is difficult to estimate the number of cases that will be reported through the CPSP. Not all cases of congenital syphilis will be seen by paediatricians and subspecialists participating in the CPSP reporting system and many neonates and infants likely fall under the umbrella of "probable congenital



syphilis” and were not captured in national reporting figures. Based on these factors, no more than 250 cases are expected over a two-year period.

Study limitations

Congenital syphilis is likely under-recognized, and as such, case-level data for undiagnosed patients is unknowable. By relying on reports from CPSP respondents, the gathered data will likely under-represent certain populations of children (e.g., children in rural areas, or children with limited access to paediatricians and paediatric subspecialists). Data elements not collected during routine care, including important points of history, physical exam, and diagnostic workup, will be absent from surveillance results. Longitudinal case-level data, which would be of academic interest, will also not be collected. However, the CPSP surveillance vehicle will be sufficient in addressing the study’s primary objectives with the above limitations taken into consideration.

Ethics approval

Health Canada and Public Health Agency of Canada Research Ethics Board

Analysis and knowledge translation

Interim analysis will be performed at the 6, 12, and 18-month marks of the study using descriptive statistics. Proportions will be analyzed using chi square tests and t-tests. Final analysis of gathered data will be completed within six months of the study’s closure.

In addition to the deliverables for multi-year studies, presentations will be made at annual international conferences. Publication in a high-impact journal, such as the *Journal of Infectious Diseases*, *Pediatrics*, or one of many public health or microbiology journals, is anticipated. Furthermore, the information gathered in this surveillance project may inform a new Canadian Paediatric Society position statement. Given the considerable lay-media attention around the “rise of syphilis,” a media article may be an effective way of sharing findings with the public. If there is local variability in the national distribution of congenital syphilis or its management, study findings may inform a targeted intervention to prevent future cases.

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