



Childhood tuberculosis

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Background

Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis* and less commonly *Mycobacterium bovis*, remains an infection of tremendous clinical and public health importance in Canada. The diagnosis and management of tuberculosis in children, especially in children under five years of age, are often particularly complex. Changes in immigration patterns from tuberculosis endemic regions, an increase in immunocompromised children due to underlying disease, treatment, or transplants, and rapidly changing patterns of microbial resistance underline the importance of studying and understanding the epidemiology and clinical history of childhood tuberculosis in Canada.

Tuberculosis is a legislated, reportable disease in all provinces and territories of Canada. On an annual basis, provincial and territorial TB programs voluntarily submit data on all reported cases of active TB disease to the Public Health Agency of Canada (PHAC). From 2000 to 2011, the total number of reported new and retreatment cases of active TB disease decreased from 1,724 to 1,607 with the overall incidence rate decreasing from 5.6 to 4.6 cases per 100,000 population. From 2005 to 2011, there was an average of 95 cases (range 75–114) of TB reported in children under the age of 15 years. Within this age group, the highest reported rate is in infants less than one year of age.¹ Existing data suggests that TB is not distributed evenly around the country and there are some areas and populations with very high rates while others are very low.



Any surveillance-based study must then take steps to adequately capture cases from the high-risk populations and areas.

The incidence of both multi-drug resistant tuberculosis (MDR-TB, resistant to both isoniazid and rifampin, the two most important first-line tuberculosis drugs) and extensively drug-resistant tuberculosis (XDR-TB, resistance to isoniazid and rifampin plus second-line tuberculosis therapy) is increasing in many parts of the world and there have been recent reports of totally drug-resistant disease in India.²⁻⁵ Based on the PHAC surveillance data, between 2000 and 2011 there were 19 cases with resistance to one of more medications, two of which were identified as MDR-TB (one each from Somalia and India) in children under 15 years of age. However, these data are based on only 31 isolates for which results were available and thus the true incidence of drug-resistant tuberculosis in Canadian children may be under-reported.⁶

While cases of tuberculosis reported to PHAC are an important source of basic information, there are several limitations to these passively collected data, the most significant being a lack of clinical, treatment, and certain outcome information. The overall goal of this study is to more fully understand and validate the epidemiology, clinical spectrum, diagnostic challenges, microbiology, BCG vaccination, and treatment response of tuberculosis in children in Canada under the age of 15 years and document any changes that occur over time.

Methods

The collection of the TB data for this project will be conducted through clinically active paediatricians and subspecialists, including infectious disease specialists and respiratory medicine specialists, who report cases through the CPSP. As non-paediatricians manage tuberculosis in children in some parts of Canada, selected individuals who are members of Canada's tuberculosis physician community will also be included in this surveillance. Participants will be questioned monthly through the CPSP regarding TB. They will receive the TB study protocol, including the surveillance case definition below, and will be asked to complete detailed questionnaires for all reported cases. Reports will be forwarded to the CPSP who will provide de-identified data to the principal investigators. With concurrence of the reporting physician, follow-up questionnaires will be sent every six months until six months after the treatment is completed to capture information on outcomes and adverse events.

Objectives

- 1) Validate TB incidence rates based on age, gender, provincial/territorial residence, origin, including First Nations, Inuit, Métis and foreign-born, as reported by PHAC.
- 2) Examine the range of clinical presentation of tuberculosis among children in Canada.
- 3) Determine the prevalence of comorbidities in children with newly diagnosed active TB disease.
- 4) Examine the role of various diagnostic methods and tools such as presumptive clinical diagnosis, traditional microbiologic and newer tests including interferon gamma release assay and polymerase chain reaction.
- 5) Examine treatment drug regimens, adherence, deteriorations during therapy in different patient populations and locations outcomes, and with different drug regimens, and adverse effects of medications.
- 6) Examine changes in drug sensitivity over time.



Childhood tuberculosis (continued)

Case definition

Report any new active or retreatment case of TB disease in patients under the age of 15 years.

Proven TB disease

1. Laboratory-confirmed

Isolation of *M tuberculosis* complex from any clinical specimen:

Positive culture **OR** positive nucleic acid amplification test (NAAT), specifically *M tuberculosis*, *M africanum*, *M canetti*, *M caprae*, *M microti*, *M pinnipedii* or *M bovis* (excluding *M bovis* BCG strain)

2. Clinically confirmed

Probable intrathoracic	Probable extrapulmonary – non-pleural
Signs and symptoms, histology suggestive of TB or close contact with an infectious source case	Signs and symptoms, histology or findings on diagnostic radiology consistent with TB
Chest radiography consistent with intrathoracic TB disease	
and at least one of the following: <ul style="list-style-type: none"> • A positive clinical response to anti-TB treatment • Documented exposure to active case of infectious <i>M tuberculosis</i> • Immunological evidence of <i>M tuberculosis</i> infection: Positive TB skin test (TST) or positive interferon gamma release assay (IGRA) 	

Presumed TB disease

Treatment for suspected TB disease at any site with at least three anti-TB drugs

Cases are identified as "New" or "Re-treatment" based on the following criteria:

- **New active case of tuberculosis disease:** No documented evidence or history of previously active tuberculosis.
- **Re-treatment case of tuberculosis:**
 1. a) Documented evidence or adequate history of previously active TB that was declared cured or treatment completed by current standards, and
 - b) At least a six-month interval since the last day of previous treatment and
 - c) Diagnosis of a subsequent episode of TB that meets the active TB case definition.

OR

 2. a) Documented evidence or adequate history of previously active TB that cannot be declared cured or treatment completed by current standards, and
 - b) Inactive disease for six months or longer after the last day of previous treatment and
 - c) Diagnosis of a subsequent episode of TB that meets the active TB case definition

Exclusion criteria

- Isolation of another pathogen, including atypical mycobacteria
- Patient arriving in Canada on TB treatment for presumed TB but for whom treatment is stopped because subsequent work-up in Canada suggests no TB
- Patient with latent TB (TST- or IGRA-positive but no clinical or radiologic abnormality)



Duration

October 2013 to September 2016. Three years of prospective surveillance and case finding and follow-up until six months after end of treatment of last case.

Expected number of cases

Approximately 100-120 cases per year in children less than 15 years.

Ethical approval

The Hospital for Sick Children Research Ethics Board
Health Canada and the Public Health Agency of Canada's Research Ethics Board
Registered with the Nunavut Research Institute

Analysis

Data will be analyzed. Patients returning to treatment after having previously defaulted will be counted as 'treatment after default'. The following limitations will be taken into account for the analysis and interpretation of study results:

Latent TB infection in childhood is much more common than disease. Childhood TB is paucibacillary and sometimes difficult to diagnose and to differentiate from latent infection. The criteria used in this study for the diagnosis of TB disease are the recently developed international norms designed to minimize diagnostic variation, but these diagnostic difficulties may still lead to variations at the level of individual clinicians or regions. This may result in changes in rates that do not reflect a change in the true incidence of disease. This caveat should not apply to the incidence of culture-positive disease.

Publication

Quarterly reports will be provided to the CPSP and PHAC regarding number of cases, geographic distribution of cases, and completions rates of questionnaires. On an annual basis, a summary of data will be provided for inclusion in the *CPSP Results* publication. Final results will be published in peer-reviewed journals and will be presented at conferences. Results of this study will also be used to inform subsequent revisions to the Canadian Tuberculosis Standards.

References

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