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CAN WE ELIMINATE TUBERCULOSIS?

Guest Editor: Elizabeth Rea

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The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

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TABLE OF CONTENTS

Tuberculosis in Canada, 2016

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Abstract

Background: Tuberculosis (TB) is a major global health problem that affected an estimated 10.4 million people worldwide in 2016. The Public Health Agency of Canada (PHAC) monitors active TB disease through a national surveillance system, which is a collaborative effort with the provinces and territories.

Objective: This article presents an epidemiological summary of the active TB disease cases reported from 2006 to 2016, with a focus on 2016. Treatment outcomes for cases diagnosed in 2015 are also presented.

Methods: The Canadian Tuberculosis Reporting System (CTBRS) is a case-based surveillance system that maintains non-nominal data on people diagnosed with active TB disease in Canada. Data are collected annually from the provinces and territories, analyzed by PHAC and validated by each province and territory.

Results: The number of active TB disease cases increased from 1,642 in 2015 to 1,737 in 2016, corresponding to an increase in incidence rate from 4.6 to 4.8 per 100,000 population. Foreign born individuals continued to make up the majority of cases reported (70%) and the incidence rate remained highest among Canadian born Indigenous people (23.5 per 100,000 population) and was particularly high within the Inuit population (170.1 per 100,000 population). Over the past decade, there was a slight decrease in the number of cases among children and the proportion of re-treatment cases declined from 8.3% of cases in 2006 to 5.4% of cases in 2016.

Conclusion: Although tuberculosis incidence rates in Canada are low in the global context and have been relatively stable over the last decade, there has been a slight increase in rates over the last three years, especially in the foreign born population which accounts for the majority of cases. The decrease in cases among children suggests less active transmission and the low proportion of re-treatment cases suggests effective treatment and adherence.

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Introduction

Tuberculosis (TB) is a major global health problem and is the leading cause of death from a single infectious agent, ranking above HIV/AIDS. Worldwide, a total of 10.4 million people were diagnosed with active TB in 2016, among whom 90% were adults and 65% were males (1). The target of the World Health Organization's (WHO) "End TB Strategy" is to reduce the global incidence from a projected 110 per 100,000 by 2015 to 10 per 100,000 or less by 2035 (2). The WHO's Action Framework for Low-Incidence Countries outlines that pre-elimination of TB (defined as <1 TB case per 100,000) should be reached by 2035, while full elimination (defined as <0.1 case per 100,000) should be possible by 2050 or before, with the introduction of new tools such as a potential new vaccine (3).

Among the G7 countries (United States (US), France, Germany, Great Britain, Italy, and Japan), Canada has the second lowest TB incidence rate (after the US) (1). Although the incidence rate of active TB disease in Canada is among the lowest in the world and has been decreasing over the past 60 years, high incidence rates persist among certain subsets of the population, including foreign born individuals and Indigenous peoples (4).

The Public Health Agency of Canada (PHAC) monitors active TB disease through the Canadian Tuberculosis Reporting System (CTBRS), a collaborative effort among the federal, provincial and territorial ministries of health. Public Health Agency of Canada uses TB surveillance data to monitor progress toward reducing the burden of TB in Canada, as outlined in *Tuberculosis Prevention and Control in Canada: A Federal Framework for Action* (5). Working with partners, the Government of Canada is taking steps to reduce the incidence of TB in high-risk populations and pave the way toward TB elimination.

This report describes the epidemiology of reported cases of active TB (new and re-treatment) in Canada between 2006 and 2016 by geographic distribution, age, sex, origin and diagnostic classification. This report is a follow-up to a previous surveillance report published for 2005–2015 (6). The 2016 results are discussed in the context of data from previous years to provide an evidence base for public health action toward elimination of the disease. Treatment outcomes for cases diagnosed in 2015 are also reported.

Methods

The CTBRS is a case-based surveillance system that maintains non-nominal data on people diagnosed with active TB disease in Canada. Details on the CTBRS's methods, including data collection processes, data management, data quality control, analysis and the classification and categorization of population subgroups, have already been described (4). However, of note is that Canada tracks cases by their origin including Canadian born (Indigenous and non-Indigenous) and foreign born. Canadian born Indigenous people comprise three distinct populations: First Nations, Inuit and Métis.

Provincial and territorial public health authorities voluntarily submit data to PHAC on all new and re-treatment cases of active TB disease that meet the Canadian case definition for national surveillance (7). Typically, treatment for fully susceptible TB lasts for six to nine months (8); therefore, treatment outcome data are submitted between 12 and 18 months following submission of the initial case report. If treatment is ongoing at the time of data submission to PHAC, the reporting jurisdiction submits an interim report followed by annual updates until the case file is closed. Data are submitted to PHAC either through manual completion of a standard reporting form or by electronic transmission. All raw data (paper forms and electronic datasets) are retained in compliance with the *Directive for the Collection, Use and Dissemination of Information Relating to Public Health* (*PHAC, 2013, unpublished document*).

Active TB disease is classified as either respiratory or non-respiratory. Respiratory TB includes pulmonary TB, TB of the pleura and TB of the intrathoracic or mediastinal lymph nodes, larynx, nasopharynx, nose and sinuses. Primary disease is characterized by pleuritis and pleural effusion due to recent (i.e., within preceding 24 months) infection with *Mycobacterium tuberculosis*. Non-respiratory TB refers to all other disease sites.

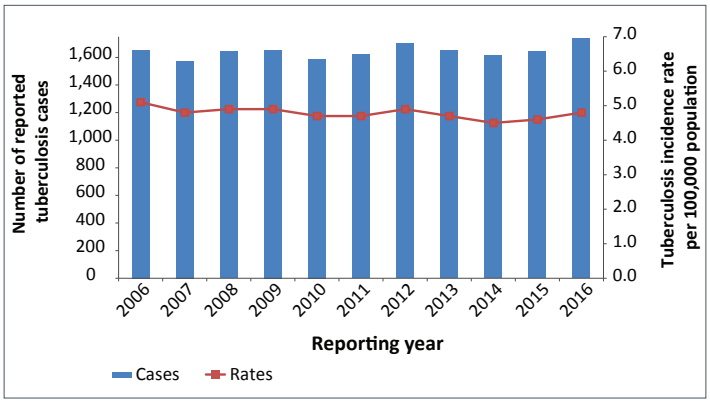
The "incidence rate" refers to individuals diagnosed with active TB disease (new and re-treatment) per 100,000 population in a given reporting year. Population denominators used to calculate rates are derived from a number of sources. For the total Canadian and provincial/territorial population counts by age and by sex, rates are based on mid-year estimations from 2011 census data produced by the Demography Division of Statistics Canada (*unpublished data*). The foreign born population counts are estimates based on Statistics Canada's 2011 National Household Survey (9). For Indigenous population groups, namely, First Nations, Inuit and Métis, rates are also based on data from the 2011 National Household Survey (10). Finally, rates for First Nations individuals with status, both on and off-reserve, were calculated using population projections of the Indian Register produced by Indigenous and Northern Affairs Canada (*unpublished data*).

Microsoft Excel 2010 and SAS Enterprise Guide (SAS EG) v5.1 software were used for data cleaning and analysis. No statistical procedures were used for comparative analyses, nor were any statistical techniques applied to account for missing data. With the exception of risk factor data, data collected through this system were virtually complete. Data in tables with small cell sizes (n=<5) were not suppressed, since disclosure was not deemed to pose any risk of identifying individual cases. These procedures are in line with the *Directive for the Collection, Use, and Dissemination of Information Relating to Public Health* (*PHAC, 2013, unpublished document*). The data were examined by the provinces and territories to ensure accuracy; some of the more detailed data were summarized in supplementary tables (7). Data for this report were extracted from the CTBRS in August 2017. Note that in 2016, British Columbia did not submit information on Indigenous status and, therefore, cases from British Columbia were identified only as either Canadian born or foreign born. Tuberculosis cases were counted by the date that the reporting jurisdiction confirmed the individual had TB. Because data at the national level are submitted annually, any updates are typically submitted 12 months following the initial annual submission.

Results

In 2016, a total of 1,737 cases of active TB disease were reported in Canada corresponding to an incidence rate of 4.8 per 100,000 population (**Figure 1; Supplementary Table 1A** (7)). The majority (93%) of cases reported were new cases, while 5% were re-treatment cases (defined as having had at least one previous diagnosis of TB disease). Previous history of TB disease was unknown for 2% of the reported cases. The proportion of re-treatment cases among all cases reported decreased over the past decade, from 8.3% in 2006 to 5.4% in 2016.

Figure 1: Number and incidence rate per 100,000 population of reported active tuberculosis cases (new and re-treatment), Canada, 2006 to 2016



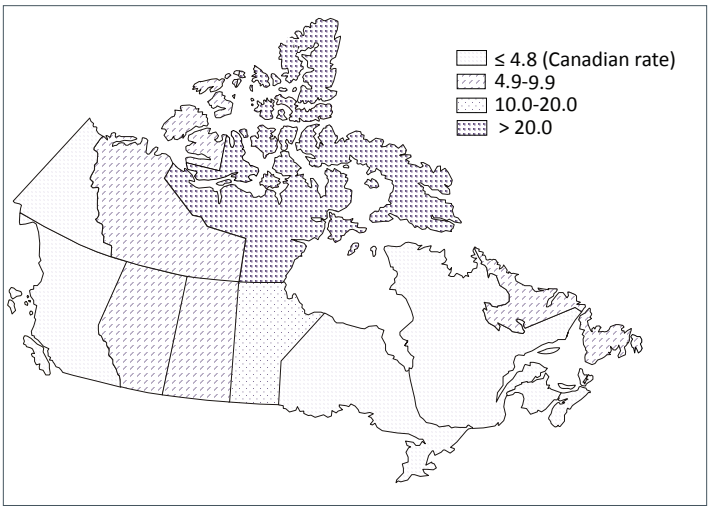
From 2006 to 2016, both the number of reported TB cases and the incidence rate remained relatively stable, from 1,653 cases reported and a rate of 5.1 per 100,000 population in 2006 to 1,737 cases and a rate of 4.8 per 100,000 population in 2016 (Figure 1).

Geographical distribution

In 2016, provincial/territorial-specific TB incidence rates ranged from 0.2 per 100,000 population in Nova Scotia to 142.9 per 100,000 population in Nunavut (**Figure 2**). The reported incidence rates in Newfoundland and Labrador, Manitoba, Saskatchewan, Alberta, Northwest Territories and Nunavut were higher than the national rate of 4.8 cases per 100,000 population. The three largest provinces, Ontario, Quebec and

British Columbia, continued to account for the majority (64%) of all reported cases in 2016.

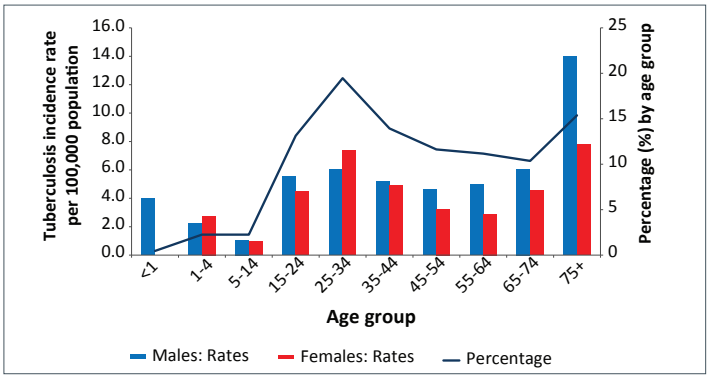
Figure 2: Tuberculosis incidence rate per 100,000 population by province/territory, Canada, 2016



Age and sex distribution

As in previous years, the largest percentage of reported cases was seen in young adults (aged 25 to 34 years). However, the highest incidence rate was observed for those aged 75 years or older, at 10.4 per 100,000 population (**Figure 3; Supplementary Tables 2 and 3** (7)). The proportion of cases reported to have occurred in people less than 15 years of age among all cases declined slightly from 6.4% (n=106/1,653) in 2006 to 5.0% (n=86/1,737) in 2016 which corresponds to rates of 1.9 per 100,000 and 1.5 per 100,000 in 2006 and 2016, respectively.

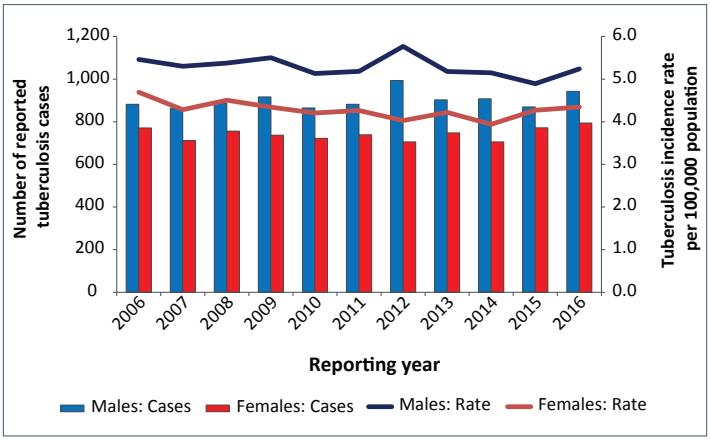
Figure 3: Tuberculosis incidence rates per 100,000 population and percentage by age group and sex, Canada, 2016



In 2016, males and females between the ages of 1 and 44 years had similar TB incidence rates, while males aged 45 years and older had higher incidence rates compared with females. For those 75 years and older, the incidence rate for males (14.0 per 100,000 population) was almost twice the rate for females (7.8 per 100,000 population).

In all years from 2006 to 2016 more males were diagnosed with TB than females. In 2016, the ratio of male to female TB cases was 1.2:1. Males accounted for 54% (n=943) of reported cases, corresponding to an incidence rate of 5.2 per 100,000 population (**Figure 4; Supplementary Table 1B** (7)). In comparison, females accounted for 46% (n=794) of all reported cases for an incidence rate of 4.3 per 100,000 population (**Supplementary Table 1C** (7)).

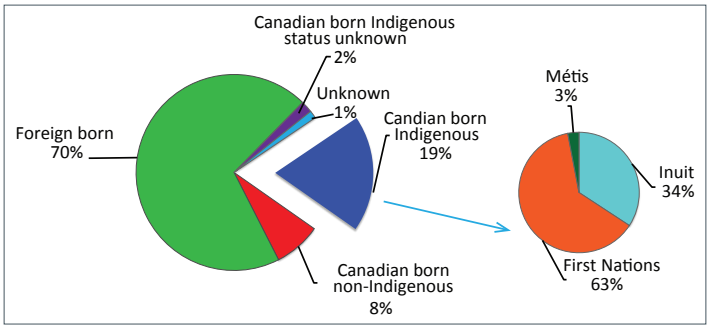
Figure 4: Number of reported active tuberculosis cases (new and re-treatment) and incidence rates per 100,000 population by sex, Canada, 2006 to 2016



Distribution by origin

Of the 1,737 cases reported in 2016, foreign born individuals accounted for 70% (n=1,213) of cases, Canadian born Indigenous people made up 19% (n=333) of cases, and Canadian born non-Indigenous people accounted for 8% (n=135) of cases; 2% (n=34) were classified as Canadian born with an unknown Indigenous status and 1% (n=22) were of an unknown origin (**Figure 5**).

Figure 5: Distribution of active tuberculosis cases (new and re-treatment) by origin, Canada, 2016



From 2006 to 2016, trends in incidence rates varied by origin group (**Table 1; Supplementary Table 5** (7)). While the rates have remained stable among Canadian born non-Indigenous and foreign born individuals, there were variations in the Canadian born Indigenous population. For example, over the past decade the incidence rate for the Inuit population increased from 115.1 to 170.1 per 100,000 population. Among First Nations living on-reserve, an overall downward trend (31.5 per 100,000 in 2006 to 20.4 per 100,000 in 2015) was observed between 2006

Table 1: Tuberculosis incidence rates per 100,000 population, by origin, Canada, 2006–2016

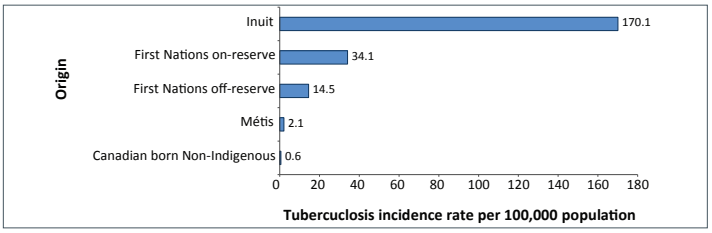
Reporting year	First Nations on-reserve	First Nations off-reserve	Métis	Inuit	Foreign born	Canadian born Non-Indigenous	Total Canada
2006	31.5	26.3	7.2	115.1	14.9	0.9	5.1
2007	29.7	24.2	7.5	85.2	14.8	0.7	4.8
2008	26.8	28.0	6.1	160.0	14.5	0.9	4.9
2009	27.0	24.3	5.4	157.1	14.4	1.0	4.9
2010	23.7	20.0	5.4	200.0	14.1	0.7	4.7
2011	21.2	16.4	4.4	166.7	14.7	0.7	4.7
2012	23.8	18.7	2.2	243.9	14.6	0.7	4.9
2013	30.8	11.4	3.5	139.4	17.4	0.6	4.7
2014	21.7	15.2	3.6	177.6	14.2	0.6	4.5
2015	20.4	11.1	2.2	164.7	14.9	0.6	4.6
2016	34.1	14.5	2.1	170.1	15.2	0.6	4.8

to 2015 except for an increase in 2013 (30.8 per 100,000) and again in 2016 (34.1 per 100,000). In comparison, the incidence rate decreased among First Nations living off-reserve (26.3 per 100,000 in 2006 to 14.5 per 100,000 in 2016) as well as among the Métis population (7.2 per 100,000 in 2006 to 2.1 per 100,000 in 2016).

Indigenous peoples

In 2016, of the 333 reported Canadian born Indigenous cases, 63% (n=209) were First Nations, 34% (n=114) were Inuit and 3% (n=10) were Métis (Figure 5; Supplementary Table 5 (7)). In 2016, compared to the incidence rate of 0.6 per 100,000 population in the Canadian born non-Indigenous population, the incidence rate among the Métis (2.1 per 100,000 population) was more than three times higher and the incidence rate among all First Nations people (23.8 per 100,000) was 41 times higher (**Figure 6**). The highest incidence rate across all origin groups was among the Inuit at 170.1 per 100,000 population; a rate which was more than 296 times higher than the rate in the Canadian born non-Indigenous population (when non-rounded numbers are used, i.e. 170.1492 / 0.57405=296.4).

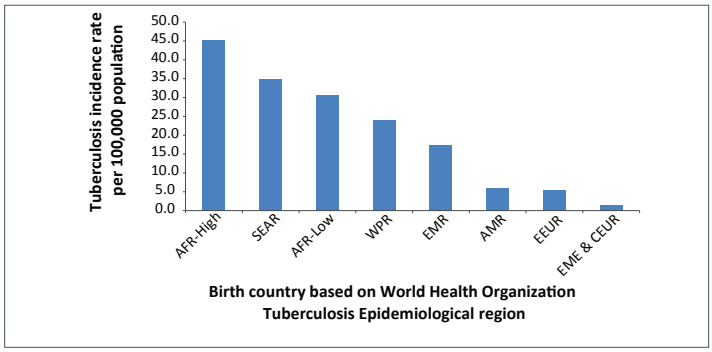
Figure 6: Tuberculosis incidence rate per 100,000 population by Indigenous population, Canada, 2016



Foreign born individuals

In 2016, the rate of TB in the foreign born population was 26 times the rate in the Canadian born non-Indigenous population. Based on birth country classified by World Health Organization TB epidemiological region (11), the two regions with the highest TB incidence rate among foreign born persons in Canada in 2016 were Africa high HIV prevalence countries (45.1 per 100,000 population), followed by South-East Asian Region (34.9 per 100,000 population) (**Figure 7**). The most prevalent countries of origin among foreign born cases reported in 2016 were India (n=257, 21.2% of all foreign born cases), the Philippines (n=252, 20.8% of all foreign born cases), China (n=105, 8.7% of all foreign born cases), Vietnam (n=68, 5.6% of all foreign born cases) and Pakistan (n=45, 3.7% of all foreign born cases).

Figure 7: Tuberculosis incidence rate per 100,000 population among foreign born cases by epidemiological region[a], Canada, 2016



Abbreviations: AFR-High, Africa high HIV prevalence; AFR-Low, Africa low HIV prevalence; AMR, American Region – Latin American countries; CEUR, Central Europe; EEUR, Eastern European Region; EME, Established Market Economies; EMR, Eastern Mediterranean Region; SEAR, South-East Asian Region; WPR, Western Pacific Region

[a] Based on birth country, which are regrouped by epidemiologic regions as specified by the World Health Organization (11)

Of the 1,213 foreign born TB cases reported in 2016, the year of arrival into Canada was known for 97% (n=1,180) of cases. Of these, 40% had arrived within the past five years and included 24% who were diagnosed with active TB in the first two years since arrival. In 2016, immigration status at the time of diagnosis was reported for 72% (n=874) of cases. Of these, 79% (n=694) were reported to be Canadian citizens or permanent residents, 9% (n=78) were temporary residents (visitors, students or foreign workers) and 4% (n=36) were refugees, refugee claimants or convention refugees. For the remaining 8% (n=66) of reported

TB cases, immigration status was reported as "other" without additional details.

Diagnostic classification

In 2016, respiratory disease accounted for 78% (n=1,349) of all diagnosed active TB cases in Canada (**Supplementary Tables 6 and 7** (7)). Similar to previous years, pulmonary disease was the most frequently reported site of disease in 2016 (69%, n=1,196). The most frequently reported site of non-respiratory disease was peripheral lymph nodes (n=198). Of the 4,180 non-respiratory cases, 56% (n=2,339) were among females compared to 44% (n=1,841) among males. From 2006 to 2016, children younger than 15 years represented 5.7% (n=1,026/18,076) of the total cases and 66.5% of the primary cases reported (n=440/662), but only contributed to 2.8% of the non-respiratory cases reported (n=118/4,180).

Treatment outcomes for 2015

Treatment outcomes were available for 99% (n=1,626/1,642) of all reported cases of active TB disease in 2015 (**Table 2; Supplementary Table 8** (7)). Of the cases for which treatment outcome data were available, 84.9% (n=1,380) were cured or had completed treatment.

Table 2: Treatment outcome for tuberculosis cases reported in 2015, Canada

Reported Outcome	n	%
Cured or completed treatment	1,380	84.9
Death before or during treatment	142	8.7
Treatment ongoing	31	1.9
Transferred	30	1.8
Absconded or lost to follow-up	17	1.0
Treatment discontinued due to adverse event	4	0.2
Other	22	1.4
TOTAL	1,626	100

Abbreviation: n, number

The proportion of treatment success (reported as cured or had completed treatment) was similar among Canadian born non-Indigenous (87%, n=146/167) and foreign born individuals (85%, n=989/1,162). There were major differences between the three Indigenous populations; treatment success was 58% (n=7/12) among Métis, 80% (n=126/157) among First Nations and 93% (n=104/112) among Inuit. Among First Nations for whom residency information was available (n=152), the proportion of treatment success was similar among those living on-reserve and off-reserve.

Discussion

Tuberculosis incidence rates in Canada have been relatively stable over the last decade; however, over the last three years, there has been a slight increase in the overall rates from 4.5 per 100,000 in 2014 to 4.8 per 100,000 in 2016. Incidence rates in all groups remained relatively stable with the exception of the Inuit who reported a 1.5-fold increase from 2006 to 2016 and the First Nations on-reserve who reported a 1.67-fold increase from 2015 to 2016 after a downward trend was observed between 2006 and 2015. The foreign born population still accounts for 70% of reported cases. Males continued to be more frequently diagnosed with TB than females at a ratio of 1.2:1. There was a slight decrease of cases among children (0–14 years old) over the past decade that suggests effective prevention and control measures have been implemented to decrease active transmission (12). Pulmonary TB remained the most commonly reported site of disease (69%). The relatively low and decreasing percentage of re-treatment cases reported reflects the low incidence of TB in Canada and suggests effective treatment and high treatment compliance (13). Treatment outcome data indicated that 85% of cases had been cured or had completed treatment.

There are several reasons that could explain the slight increase seen in the overall incidence rates over the past few years: small number variation; reactivation of TB; focal outbreaks; and/or increased detection due to active case finding efforts. Continuous monitoring and further analysis are required to understand if such changes are statistically significant or not.

Despite the low rate of incidence and transmission in the general population, Canada recognizes the need for new targeted strategies both to address the high incidence of active TB disease that persists in Indigenous peoples and foreign born individuals and to achieve the TB pre-elimination goal for low-incidence countries (<1 per 100,000 by 2035) (3,4). Outbreak control in Northern Inuit communities is underway (14). One of the priority action areas outlined in WHO's Action Framework for low-incidence countries is to undertake screening for latent TB infection (LTBI) in TB contacts and selected high-risk groups, and to provide preventive treatment to persons with LTBI who are at greatest risk of developing active TB disease (3). Although Canada does not have a national surveillance program in place for LTBI, initiatives are underway that will contribute to a better understanding of the prevalence of LTBI across Canada.

Data limitations

The data included in this report are subject to a few limitations. Because the CTBRS is a passive surveillance system, it relies on data collected retrospectively from medical and laboratory records as opposed to active case solicitation. As a result, it is difficult to ascertain whether all people with active TB disease are being identified and reported. However, the World Health Organization estimates that Canada's surveillance system has a case detection rate of 92% with a range of uncertainty of 80% to 110% (1). The accuracy of the data is partially a function of timely reporting and updates to PHAC from the provinces and territories. Some degree of lag does occur, creating a reporting delay.

It needs to be noted that the province of British Columbia transitioned to a new provincial/federal public health IT system (Panorama) in 2016. British Columbia reported a slight decrease in the number of cases and incidence rate in 2016 which may be partially attributed to data inconsistencies resulting from data

conversion (Personal communication with David Roth, October 27, 2017). These potential inconsistencies are being identified and addressed, and the situation may be corrected over time.

Annual updates on the number of cases of active TB in Canada and corresponding incidence rates are important in monitoring progress toward the goal of reducing the burden of TB in Canada. The data in this report are considered provisional and subject to change in future iterations of *Tuberculosis in Canada* surveillance reports. Differences between the data published in this report and the data published in previous national, provincial and territorial surveillance reports may be due to reporting delays or differences as to when the data were extracted from various surveillance databases. The reporting province or territory may update its published data on a more regular basis. Should differences exist between this report and provincial or territorial reports, readers are encouraged to contact the provincial/territorial jurisdiction for clarification.

Conclusion

Although tuberculosis incidence rates in Canada are low in the global context and have been relatively stable over the last decade, there has been a slight increase in rates over the last three years, especially in the Inuit population, and the foreign born population still accounts for the majority of cases. Further monitoring and analysis is needed to understand if this increase marks the start of a trend. The decrease in cases among children suggests less active transmission and the low proportion of re-treatment cases suggests effective treatment and adherence. The federal government, in partnership with provincial and territorial governments and other federal departments and agencies, continues to work towards enhancing current efforts to prevent and control active TB disease and fostering collaborative action to address the underlying risk factors for tuberculosis in Canada.

Authors' statement

JV – Conceptualization, Validation, Formal analysis, Writing-original draft, Writing-review and editing
VG – Methodology, Software, Validation, Formal analysis, Writing-review and editing
WS – Conceptualization, Writing-review and editing, Supervision

Conflict of interest

None.

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Addressing tuberculosis among Inuit in Canada

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Abstract

The average annual rate of tuberculosis (TB) among Inuit in Canada is now more than 290 times higher than Canadian born non-Indigenous people. How did this happen? Using the Territory of Nunavut as a case example, the roots of this situation can largely be traced back to social determinants of health and challenges in access to health care. Half (52%) of all Nunavut residents live in social housing, often under overcrowded conditions. Many experience food insecurity, with food prices in Nunavut that are twice those in southern Canada. Sixty percent of Nunavut residents smoke. Challenges in health care delivery include the small isolated communities, with few roads and difficult weather conditions during the long winters, which impede the ability to reach or provide healthcare, staff that arrive with little TB experience or cultural knowledge, multiple competing health care demands, limited resources and high staff turnover. The housing shortage is not only a social determinant of health, it also impacts the ability to hire new staff or mount an effective response in the event of an outbreak.

Yet despite these challenges, progress has been made. Tuberculosis care in Nunavut includes active case finding, contact tracing for all cases of infectious TB, and screening of school age children. Rapid testing with the GeneXpert© platform has resulted in a quicker diagnosis of active TB, earlier treatment (preventing progression of disease) and less transmission. Progressively, there has been a switch from plain film to digital x-rays reducing x-ray turnaround time from as long as two to three weeks to one or two days. Standard treatment protocols include quadruple therapy until sensitivities are known, the use of home isolation for active cases and directly observed treatment (DOT) for both latent and active TB. Special access to rifapentine (Priftin), and its use in combination therapy (3HP), requires only once weekly treatments that can be completed in 12 visits instead of 78 visits for isoniazid (INH) or 120 visits for rifampin, which increases adherence and greatly reduces the health care resources needed to treat TB.

In October 2017, the Honourable Jane Philpott, then Minister of Health and now Minister of Indigenous Services, and Natan Obed, president of Inuit Tapiriit Kanatami (ITK) announced the establishment of a Task Force to develop an Inuit TB Elimination Action Framework, accompanied by regional action plans. It is hoped that the task force, and current efforts in Nunavut, will lead to the long term changes needed to ultimately eliminate TB among Inuit in Canada.

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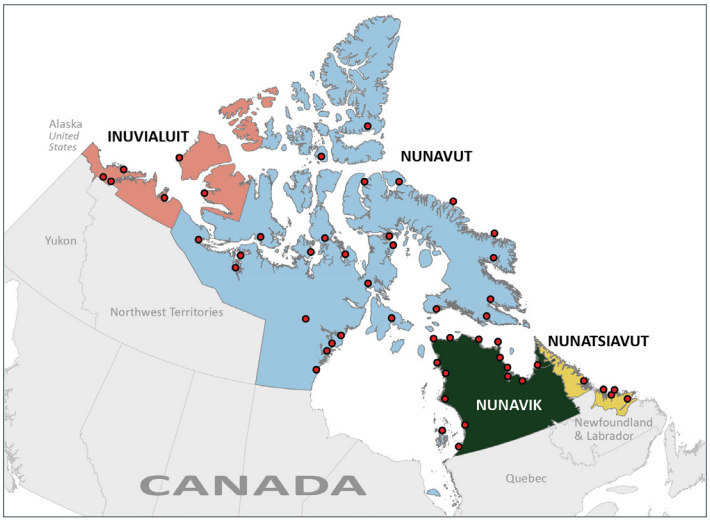
Introduction

Tuberculosis (TB) is an ongoing problem for the Indigenous peoples of Canada, especially among Inuit. The average annual rate of TB among Inuit in Canada is now more than 290 times higher than Canadian born non-Indigenous people (1). This is clearly reflected in the Territory of Nunavut, which is 85% Inuit and has a population of approximately 38,000 people. The number of cases in 2017 is likely to surpass the annual number of cases since 2010 (when the number of cases peaked at 100). Preliminary data for 2017 show that there were 100 newly diagnosed cases of active TB, at least 300 cases of latent TB and two deaths, out of a population of approximately 38,000 individuals. Sixty-eight per cent (n=17) of the 25 communities in Nunavut reported at least one case of latent or active TB (*M Patterson, unpublished data, 2017*).

The traditional homelands of Inuit in Canada (Inuit Nunangat) are currently divided into four regions: Nunatsiavut, Nunavik, Nunavut and Inuvialuit (**Figure 1**). Nunavut represents the only portion of Nunangat that, as a territory within Canada, is entirely self-governing. Nunavut accounts for approximately 20% of Canada's land mass and 0.01% of the population. All full time residents live in one of 25 communities. Although there are some significant differences in health status throughout Nunangat there are also some common themes in all four regions: life expectancy is lower than the Canadian average; there is a lack of housing; food insecurity is widespread; and unemployment is higher than the national average.

Figure 1: Four regions of the traditional homelands of Inuit in Canada (2)



Background

Previous attempts to eradicate TB in Inuit Nunangat failed, as they were plagued by health care measures that were neither culturally appropriate nor sustainable. In the 1950s, for example, the focus of TB care was on transporting individuals with active TB to the south to sanatoria, usually for years, and many never returned (3). Most Inuit are aware of relatives who disappeared in this process and even now are unable to find out exactly when or where they died or, in some cases, even where they were buried (4). Starting in the 1970s, there was a mass treatment campaign involving healthcare providers who visited communities, undertook mass screening and offered treatment to all who were found to have TB (3). When rates of TB decreased, these efforts were abandoned. Within one or two decades of discontinuing community-based screening and treatment intervention campaigns, rates of TB for all Canadian Inuit began to rise again. Thus, there is a history of exerting a significant effort to combat TB when rates are elevated then retreating when rates decline. For this reason, a sustained decline in TB rates among Inuit has remained elusive.

Because Nunavut has the highest rate of TB in Canada, and the majority of the population is Inuit, this paper will focus on Nunavut as an illustrative case example. We will describe the root causes of the high TB rates in Nunavut and describe the ongoing efforts to improve TB care. This reflects in part what is occurring in other regions of Inuit Nunangat and elsewhere in Canada.

Understanding the root causes

The high rates of TB among Inuit are rooted in social determinants of health and inequitable access to health care.

Social determinants

In terms of social determinants of health, life expectancy of Inuit (also called Nunavummiut in their language, Inuktitut) is approximately 10 years shorter than the Canadian average. For residents of Nunavut especially Inuit, inadequate housing and food insecurity remain significant problems. Half (52%) of all Nunavummiut live in social housing and, depending on the community, up to 72% of those are living in overcrowded housing (5). Housing can be so crowded that some residents sleep in shifts, as it is all too common for more than 20 people to call a 4-bedroom house a home (5). Many Nunavummiut experience food insecurity. Food prices in Nunavut are, on average, twice those in southern Canada (6). Food is also limited in terms of choice, and occasionally further limited by the inevitable difficulties of transporting food long distances by air.

Unlike many other Indigenous groups in Canada, tobacco use was not a significant part of Inuit culture prior to contact with European cultures. Since that time, smoking has increased to the point where at least 61% of Nunavummiut smoke cigarettes (7), a statistic which alone increases the risks for respiratory tract infections, including TB.

Access to health care

Health care delivery in Nunavut faces many challenges. Most Inuit live in small, remote, coastal communities. There are no road connections within Nunavut, creating what has been called the "tyranny of distance" (8), which affects all aspects of health care. Furthermore, the long, severe winters during which some communities experience several weeks or more of continuous darkness make reaching or offering health care services that much more difficult. Most health care staff have been trained in southern Canada where they may have never seen a case of TB. When the southern health care workers first arrive, they are often unfamiliar with the language and culture, making effective communication with Nunavummiut difficult.

There are many pressing health problems among the Inuit that are managed with finite health care resources. Thus, although it is imperative that TB prevention and control be addressed, it is important that TB efforts do not take away from other health care efforts, as shifting existing staff to TB efforts would lead to vulnerabilities in other areas of health. Lack of adequate space, both work and housing, also present challenges to improving the delivery of TB care in Nunavut. The housing shortages in many communities affect Nunavut's ability to hire new staff and to mount an effective surge response in the event of an outbreak.

Current situation in Nunavut

Despite the challenges, Nunavut has made some progress in improving TB care. Current practices for TB care in Nunavut include use of home isolation for active cases, and directly observed therapy (DOT) for all aspects of TB treatment (both latent and active TB). There is active case finding (including contact tracing) for all cases of infectious TB and screening for school age children (kindergarten to grade six).

Current treatment regimens for active TB includes quadruple therapy (rifampin, isoniazid [INH], pyrazinamide and ethambutol) for most cases until sensitivities to these TB drugs are confirmed. The reasons for this is there have been few cases of INH resistance in Nunavut, and during most outbreaks, many infected individuals have had multiple contacts identified as potential sources, making it impossible to guarantee who was their actual source case.

Recent progress

In April 2017, a full time TB nurse educator was hired. This has increased our ability to train new staff in TB care. Providers new to TB care have the opportunity to spend several days in Iqaluit participating in both didactic learning on TB and getting exposure to the Nunavut TB program.

In the fall of 2017, Health Canada announced approval for adding rifapentine (RPT) to the List of Drugs for Urgent Public Health Need. Prior to this, research was conducted in Ottawa and Iqaluit on a 12-dose regimen of weekly RPT plus INH (3HP) administered by DOT for the treatment of latent TB infection (9). The advantage of 3HP to both patients and the health care system is that 3HP requires one weekly visit for only 12 weeks, instead of the 78 visits required for INH or 120 visits for rifampin. This will likely be better accepted and easier to complete for individuals with latent TB infection, and will also greatly reduce the health care resources needed to treat TB.

A rapid TB diagnostic test, the Xpert MTB/RIF test© (Cepheid Inc, Sunnyvale, CA), a cartridge-based automated, nested, real-time polymerase chain reaction (PCR) test utilizing the GeneXpert© platform, has been in use in Nunavut since 2012. Initially part of a research program, this test has now become widely available to test sputa for many residents of eastern Nunavut for the presence of TB. It has been shown that quicker diagnosis of active TB results in earlier treatment (preventing progression of the disease) and less transmission of TB (10). These results have the potential to translate into significant benefits for patients and the health care system.

Other efforts underway to improve the overall health care system in Nunavut have also resulted in improvements to TB care. The most obvious example of this is related to the implementation of digital x-ray. Until relatively recently, most communities in Nunavut relied on plain film x-rays. After development in the community, films were shipped to radiologists in southern Canada for interpretation. This simple switch from film to digital has decreased x-ray turnaround time from as much as two to three weeks to one or two days. It is hoped that by the end of 2018 all 25 communities in Nunavut will have completed the transition to digital x-ray machines. In addition, Nunavut Health has an established nicotine cessation program that focuses on education and support to encourage all Nunavummiut to quit smoking.

Discussion

Tuberculosis rates are high among Inuit in Canada, and this is clearly illustrated in Nunavut. There is a long history to this, and social determinants of health and challenges with access to health care continue to contribute to this. But progress is being made. Advances in detection, diagnosis and treatment have all been integrated into TB care in the North. It is possible that the recent increase in TB rates is in part due to increased detection. With continued efforts these rates should then begin to drop.

Next steps

In light of the high rates of TB in Nunavut, and throughout Inuit Nunangat, a meeting was held October 4–6, 2017 in Ottawa, to discuss the issues (11). The meeting was jointly hosted by the Government of Nunavut and Inuit Tapiriit Kanatami (ITK), a national organization representing all Canadian Inuit. The work of ITK includes research, advocacy and education that affect Inuit living in Canada (12). The meeting brought together representatives from federal, provincial and territorial governments, clinical TB experts and researchers to exchange ideas and strategies on improving TB care for all Inuit.

At the conclusion of this joint ITK-Nunavut-hosted meeting, the Honourable Jane Philpott, then Minister of Health and now Minister of Indigenous Services, and Natan Obed, President of ITK, announced the establishment of a Task Force to develop an Inuit TB Elimination Action Framework, accompanied by regional action plans.

Regional planning is important. Although the root causes of increased rates of TB are very similar throughout Nunangat, there are significant differences between regions in terms of the challenges faced and the solutions needed to address TB. The health care systems of each region reside in very different regulatory environments, and face a variety of logistical challenges. The result is that although each region has the same end goal of eliminating TB, the regional programs will have significant differences in their approaches.

Conclusion

With the current rates of TB in Nunavut and Nunangat, a robust, enduring territorial-wide TB program is needed. There is a history of putting in significant effort to improve numbers when TB flares, then backing off when the number of cases decline. For a sustained decline in TB rates, dedicated TB staff are needed; not just for now but for years to come. It is hoped that the current efforts in Nunavut, and those undertaken by the TB Task Force, will lead to the long term changes needed to ultimately eliminate TB among Inuit in Canada.

Conflict of Interest

None.

Acknowledgements

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A cluster of tuberculosis cases linked to smoking: An under-recognized challenge for tuberculosis elimination

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Abstract

Background: Smoking is known to increase the risk of tuberculosis (TB) infection, active TB disease, relapse following treatment and death from TB, but its significance is often underappreciated as a potentially reversible risk factor in public health and clinical TB practice in Canada.

Objective: To review the current evidence on smoking and the risk of TB, describe a cluster investigation of local TB transmission related to smoking in Toronto, Ontario, and discuss the practical implications of smoking for TB elimination in Canada.

Investigation and public health response: Three TB cases were identified at the same workplace over a two year period. All three strains matched on genotyping. Extensive interviews with the cases and workplace / building managers confirmed that the three cases did not work or socialize together. The only epidemiologic link identified was that all three were regular smokers and used the same location outside the building for smoke breaks. A building ventilation assessment confirmed that unfiltered air was not recirculated between floors. Based on the epidemiological and laboratory evidence, we determined that transmission likely occurred at the partly-sheltered smoking area outside of the worksite. We established and advertised an active case-finding clinic on-site to all workers who frequented smoking areas near the building. Of 60 individuals screened with tuberculin skin testing (TST), no additional active TB cases were identified. One Canadian born person was found to be TST positive. We also offered TB education sessions to all staff in the building, and used the opportunity to promote smoking cessation for interested individuals.

Conclusion: This cluster shows compelling evidence for smoking-related transmission of TB in Toronto. The World Health Organization has called for integration of anti-smoking efforts as a key strategy toward TB elimination. Opportunities to integrate smoking and TB work in Canada include assessment for smoking-related transmission during contact investigations, routine use of smoking cessation supports for contacts and others with latent tuberculosis infection as well as those with active TB, and public health outreach.

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Introduction

Smoking as a risk factor for tuberculosis (TB) has been suspected for a hundred years and well established for several decades (1-3). Smoking interferes with multiple biological mechanisms which are important for defense against both initial infection with TB and subsequent development of active TB disease. These include impaired clearance of secretions in the airways, impaired functioning of pulmonary macrophages and CD4 cells, and decreased production of interferon gamma and Tumor Necrosis Factor-alpha (4-6). Smoking is associated with increased risk of TB infection, of active TB disease, relapse following treatment and death from TB (**Table 1**). This increased risk has been documented across a wide range of settings and populations, for active and second hand smoke (10-12).

Table 1: Summary of evidence for the increased risk of tuberculosis from smoking

Increased risk	Evidence
TB infection (1)	Pooled odds ratio: 1.83, 95% CI, 1.49–2.23
Active TB disease (2)	Relative risk: 2.29, 95% CI, 1.93–2.71[a]
Relapse following treatment (8)	Adjusted hazard ratio: 2.04, 95% CI 1.22–3.41[b]
Death from TB (9)	Relative risk: 4.5, 95% CI 4.0–5.0

Abbreviations: CI, confidence interval; TB, tuberculosis
[a] With a dose-response relationship (7)
[b] For those smoking >10 cigarettes/day compared to non-smokers

These modest relative risks—approximately double the risk for non-smokers—can have a major impact on a population scale. The World Health Organization (WHO) estimates that indirectly, smoking causes 20% of the global TB burden (3): one large study calculated the population attributable risk from smoking is as high as 38% of all TB cases for men in India (13). Despite this evidence, in our experience smoking status is often not routinely addressed in local TB management activities. While the *Canadian Tuberculosis Standards* and the national *Guidance for Tuberculosis Prevention and Control Programs in Canada* both identify smoking as a risk factor for TB, neither include smoking interventions explicitly in their recommendations for clinical care or for programmatic TB prevention work (14,15).

In the general Canadian population, the smoking rate is 18% (16), but this rate is much higher in some groups that also have higher TB rates, such as homeless populations and many Indigenous communities (17,18). However, smoking can be problematic for those at risk of TB in any population.

Toronto, Ontario has about 300 cases of active TB disease annually. Over 90% of individuals with TB were born outside Canada, as are half of all Toronto residents (19,20). We describe a cluster of TB transmission related to smoking in Toronto, Ontario and identify the public health program and clinical implications.

Cluster description

The first case in this cluster was a 34 year old male born in India who developed symptoms about a year after immigration. He was diagnosed with sputum smear 4+ cavitary pulmonary TB in July 2015 and reported smoking heavily. He lived alone. Two workplace contacts were identified but both were lost to follow-up. Over the next two years, two additional TB cases were diagnosed who worked in the same location: a large multi-employer office building with a total of approximately 1,200 workers.

Case #2 was a 55 year old Canadian born male with no significant history of travel or TB exposure. At diagnosis in December 2016, he was sputum smear 2+ and had an abnormal non-cavitary chest x-ray. He reported smoking two packs per week. He worked in the same building as Case #1 (but on a different floor), did not socialize with others in the building and worked and ate alone.

Case #3 was a 52 year old male born in India, diagnosed April 2017. He was sputum smear 1+ at diagnosis, had an abnormal non-cavitary chest x-ray and reported smoking one pack per week. He worked on the same floor as Case # 1 but in a different area. Case #2 and #3 were not named contacts of each other or of Case #1.

Genotyping results

Genotyping by mycobacterial interspersed repetitive units (MIRU)-24 and spoligotyping of all three TB isolates was identical. Whole genome sequencing of sputum samples indicated that Cases #1 and #2 had a single nucleotide variance (SNV) difference and Case #1 and Case #3 had five SNV differences (i.e., Cases #2 and #3 were six SNV differences apart), suggesting Case #1 was the source case for both Cases #2 and #3.

Public health investigation and response

At the time of investigation, Case #1 was no longer in the country; however, based on re-interviewing of Cases #2 and #3 as well as workplace and building managers, no work or social links could be identified between the three cases other than that they were all regular smokers. All three made frequent use of the same partly-sheltered location near the front entrance of the building for smoke breaks.

A building ventilation assessment confirmed that unfiltered air was not being recirculated between floors; this suggested that transmission via circulating air within the building was unlikely. Based on the epidemiological and laboratory evidence, we determined that transmission likely occurred from Case #1 to both Cases #2 and #3 in the outdoor smoking areas at the worksite.

As transmission had occurred among smokers who were not identified as friends, and no contact list was available to identify those at risk, a site-based approach was used to expand contact follow-up. We established and advertised an active case-finding clinic on-site to all employees in the building (systematic screening for active TB in a pre-determined target group), offering tuberculin skin test (TST) testing and sputum collection to smokers and non-smokers who frequented smoking areas near the building from the time Case #1 was infectious to the time of the investigation. Of 60 individuals screened, no additional active TB cases were identified. One TST converter was identified and counselled on latent TB infection (LTBI) treatment. We also offered TB education sessions to all staff in the building, and used the opportunity to promote smoking cessation for interested individuals.

Discussion

This cluster shows compelling evidence for smoking-related transmission in Toronto; these three cases had no other connection, and were not from marginalized communities (though the index case was born in a high-burden country). It is particularly disconcerting that transmission occurred outdoors.

In our experience, smoking is often under-recognized—and smoking interventions under-applied—in public health TB programs as well as clinical TB care.

In practical terms, there are four main strategies for integration of smoking issues in TB work:

- assessing smoking transmission risk as part of contact investigations
- incorporating smoking cessation interventions routinely as an adjunct to prevent active TB among contacts and others with LTBI
- improving clinical outcomes for those with active TB disease
- implementing strategic anti-smoking outreach for high-TB risk populations, in collaboration with substance use prevention programs

The risk of TB transmission is known to be higher in crowded and/or under-ventilated environments (14). The most extreme example of this increased risk of exposure related to smoking is "hot-boxing", where people smoke together in a small confined space (a car or small room) to concentrate marijuana or other smoke in the air and increase the resulting high. Several outbreak investigations have identified smoking marijuana (21,22) and crack cocaine (23) as a risk for transmission.

Although specific populations might be at particularly high risk for smoking-related TB transmission, due to crowding in combination with high smoking rates, our experience in Toronto

shows it can occur even in a large city with overall lower smoking rates and among non-marginalized individuals. The cluster described in detail above is not the only recent example of smoking-related TB transmission in Toronto. In the last two years we have also documented TB genotype-confirmed transmission related to a shisha (hookah) lounge (one case), tobacco/marijuana hot-boxing (cluster of six cases, three of whom are also household contacts) and a designated smoking balcony at a homeless shelter (three cases).

Outdoor exposures are generally thought to be very low risk for TB transmission (14). Our case study illustrates that TB transmission can happen even outdoors, particularly in confined spaces with an overhang, the kind of partly-enclosed spaces outside buildings used by many workplace smokers to shelter from the weather. Frequent short exposures during smoke breaks can add up to substantial TB risks for people who smoke regularly together with an infectious individual, even without additional social interaction.

Contact follow-up may be more difficult for such informal smokers groups; there is no registration and participation is often fluid. Smokers may not think of others who are present at informal smoking locations as friends or social contacts. Instead of asking "Who do you smoke with?" it may be more helpful to frame the question as "Who else is there when you are smoking?" Both tobacco and marijuana users may also be reluctant to self-identify or implicate others in an activity that is not always socially accepted (or legal). Site-based screening and creative outreach approaches tailored to the situation may be helpful. The decriminalization (and potential increased use) of marijuana in Canada in 2018 is unlikely to pose a TB risk for most Canadians, but serious consideration should be given to monitor the impact in high-TB burden communities and populations.

People with LTBI who smoke are more likely to benefit from LTBI treatment, because their relative risk for developing active TB is higher than for non-smokers. More explicit attention to this risk factor in routine counselling/clinical care, especially for TB contacts, may help to increase uptake of LTBI treatment. Similarly, smokers with LTBI would also benefit from cessation counselling and referral as a routine part of LTBI care regardless of the decision about LTBI treatment. Individuals with active TB disease who smoke are at risk for worse outcomes, and would also benefit from smoking cessation support.

Strategically, as for populations with high rates of diabetes, TB programs might collaborate with smoking/substance use prevention programs to develop tailored, culturally appropriate smoking prevention and cessation initiatives for local groups with higher TB and smoking rates. These may be Indigenous or homeless communities, but also some immigrant groups. Nationally, the large pool of LTBI—mainly among foreign-born individuals—drives most of the TB in Canada (24). Our cluster also highlights the importance of local by-laws and workplace health and safety related to smoking; many worksites do not permit smoking around building entrances, but we are not aware of specific prohibitions against smoking in partly-enclosed sheltered areas nearby.

Most critically, smoking may be under-recognized in Canada as an escalator of forward TB transmission, particularly in some of the communities most affected by TB outbreaks: homeless populations, northern First Nations reserves and Inuit communities. These are settings where high TB incidence rates, high prevalence of smoking and crowded indoor spaces co-exist and can lead to explosive transmission. The 2012 Aboriginal Peoples Survey found that 52% of Inuit aged 15 years or older smoked cigarettes daily, almost three times the general Canadian rate (25). The Inuit population also has the highest rate of active TB disease in Canada: 170/100,000 in 2016. This is more than 290 times the rate of active TB disease in Canadian born non-Indigenous people (26). Because the highest risk of active TB disease is in the first two years following infection (14), in situations where smoking is widespread, the higher rate of both TB transmission and progression to active TB disease among smokers can also lead to rapidly evolving clusters of new cases. In this context, integration of TB and tobacco/substance use work across programmatic silos may be helpful. Tuberculosis programs in Nunatsiavut, Newfoundland and in Nunavik, Quebec—both experiencing TB outbreaks—recently developed outreach initiatives incorporating marijuana harm reduction messages, developed in collaboration with community youth (personal communication, T. Buckle and Dr. F. Bouchard, October 4, 2017).

Smoking is one of few potentially reversible risk factors for TB, and affects multiple points in the natural history of the disease. There have been calls from the WHO and others for clinical and program-level integration of anti-smoking and TB elimination work (3,6). We believe there are multiple opportunities to do this in Canada. Interventions to decrease smoking may help to decrease local transmission and reduce the number of new cases in southern cities as well as in the north.

Authors' statement

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Conflict of interest

None.

Contributors

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Summary of the NACI Update on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis (Tdap) Vaccine

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Abstract

Background: In Canada, pertussis is an endemic and cyclical disease, with peaks occurring at two- to five-year intervals. Although pertussis incidence varies by age group, unvaccinated or undervaccinated infants are at greatest risk of infection and associated complications. Since the last National Advisory Committee on Immunization (NACI) recommendations published in 2014, new evidence on the safety and effectiveness of tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis (Tdap) vaccine administration in pregnancy has become available.

Objective: To provide guidance on maternal immunization in pregnancy as a strategy to reduce disease incidence and severe outcomes (defined as hospitalization or death) from pertussis infection in infants less than 12 months of age.

Methods: The NACI reviewed evidence on the burden of disease in Canada, vaccine safety and immunogenicity and vaccine effectiveness in jurisdictions that have implemented maternal immunization programs. A total of 59 articles were identified, retrieved and included in the literature review to inform this statement.

Results: In the majority of reviewed studies, post immunization increases in antibody levels resulted in more than 90% of women achieving anti-PT levels greater than or equal to 10 IU/ml one month following immunization. In infants, maternal immunization was found to result in increased pertussis antibody concentrations. In the majority of studies, following the receipt of the fourth diphtheria, tetanus and pertussis (DTaP) dose after 15 months of age, no statistically significant differences in antibody levels and avidity were observed between infants whose mothers received Tdap in pregnancy and those whose mothers did not receive Tdap in pregnancy. No major maternal or infant safety issues, including pregnancy outcomes, were reported in the reviewed literature. Effectiveness of maternal Tdap immunization in pregnancy was estimated to be over 90% against pertussis in infants younger than two months of age, with no deaths observed among infants whose mothers received Tdap prior to 36 weeks of pregnancy. Maternal immunization with Tdap in pregnancy also resulted in a reduction in infant disease severity and hospitalization. Vaccine effectiveness was also reported to persist after the receipt of the first three DTaP doses, with immunization in pregnancy resulting in additional protection of up to 70% in children whose mothers received Tdap in pregnancy.

Conclusion: There is now strong evidence to support the NACI recommendation that immunization with Tdap vaccine should be offered in every pregnancy. This is ideally administered between 27 and 32 weeks of gestation but evidence also supports providing maternal Tdap over a wider range of gestational ages, from 13 weeks up to the time of delivery, in view of programmatic and unique patient considerations.

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Introduction

In Canada, pertussis is an endemic and cyclical disease, with peaks occurring at two- to five-year intervals. Although pertussis incidence varies by age group, unvaccinated or under vaccinated infants are at greatest risk of infection and associated complications. Between 2006 and 2015, the average age-specific incidence rates and hospitalization rates were highest among

infants less than one year of age (71.2 and 33.6 cases per 100,000 population). Between 2006 and 2016, infants less than two months of age accounted for the largest proportion of special care unit (SCU) admissions (40.5%), followed by infants three to four months of age (21.4%).

Lack of maternal immunity is assumed to increase an infant's susceptibility to infection, both by increasing the risk of disease in mothers (and subsequent transmission to the infant) and by providing insufficient passive protection through antibody transfer (via the placenta or via breast milk). A recently-conducted serosurvey found that the majority of pregnant women (more than 90%) in Canada had undetectable anti-pertussis toxin levels. In a 2017 survey of immunization practices in Canada, the majority of provincial and territorial governments reported logistical difficulties with implementing maternal tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis (Tdap) vaccine immunization programs during outbreak settings only.

Since the last National Advisory Committee on Immunization (NACI) recommendations were published in 2014, new evidence on the safety and effectiveness of Tdap administration in pregnancy has become available. In accordance with the direction that was provided by the Canadian Immunization Committee, NACI reviewed the following:

- the burden of pertussis in infants less than 12 months of age
- the safety of maternal immunization with Tdap vaccine in pregnancy
- the efficacy and effectiveness of maternal immunization with Tdap in pregnancy in preventing severe outcomes of pertussis infection in infants less than 12 months of age
- the effects of maternal Tdap immunization in pregnancy on an infant's immunological response to the primary vaccine schedule; and
- the impact of maternal Tdap immunization in pregnancy on long term protection against pertussis in children

The objective of the Statement Update was to provide guidance on maternal immunization in pregnancy as a strategy to reduce disease incidence and severe outcomes (defined as hospitalization or death) from pertussis infection in infants younger than 12 months of age. The full update is available online (1). This article is a summary of the update's key findings.

Methods

NACI reviewed evidence on the burden of disease in Canada, vaccine safety and immunogenicity and vaccine effectiveness in jurisdictions that have implemented maternal immunization programs. A total of 59 articles were identified, retrieved and included in the literature review to inform this statement. Epidemiological analysis was conducted using national surveillance data including the Canadian Notifiable Disease Surveillance System (CNDSS), the Immunization Monitoring Program Active (IMPACT) and the Canadian Institute for Health Information Discharge Abstract Database (DAD). The evidence pertaining to the following questions was reviewed and critically appraised:

- Is there a significant difference in local or systemic adverse events for the mother following immunization with Tdap vaccine in pregnancy (all stages) compared with adult immunization outside pregnancy?
- Is there a significant difference in adverse fetal and neonatal health outcomes for the baby following immunization of their mother with Tdap vaccine in pregnancy?
- Is maternal immunization in pregnancy with Tdap significantly more efficacious or effective in preventing severe disease in infants under 12 months of age compared with no maternal immunization in pregnancy?
- Is the immunogenicity of diphtheria, tetanus and pertussis (DTaP) vaccination in children born to mothers immunized with Tdap vaccine in pregnancy significantly different compared with infants born to mothers who were not immunized with Tdap vaccine in pregnancy?
- Does maternal immunization with Tdap in pregnancy significantly impact efficacy or effectiveness of DTaP vaccines in preventing related disease in children younger than four to six years of age? A detailed analysis of the literature was published in a separate NACI literature review (2). An evidence synthesis and overall summary of the literature, along with specific recommendations, were provided in the NACI Statement Update (1).

Results

Immunogenicity

In the majority of reviewed studies, post immunization increases in antibody levels resulted in more than 90% of women achieving anti-PT levels greater than or equal to 10 IU/ml at one month following immunization. While no serologic correlate of clinical protection against pertussis currently exists, anti-PT levels greater than or equal to 10 IU/ml are considered to be protective against severe disease. In infants, maternal immunization was found to result in increased pertussis antibody concentrations, with avidity increasing linearly with time to delivery. In the majority of studies, following the receipt of the fourth DTaP dose after 15 months of age, statistically significant differences in antibody levels and avidity were not observed between infants whose mothers received Tdap in pregnancy and those whose mothers did not receive Tdap in pregnancy.

Safety and effectiveness

No major maternal or infant safety issues, including pregnancy outcomes, were reported in the reviewed literature. Effectiveness of maternal Tdap immunization in pregnancy was estimated to be over 90% against pertussis in infants younger than two months of age, with no deaths observed among infants whose mothers received Tdap prior to 36 weeks of pregnancy. Maternal immunization with Tdap in pregnancy also resulted in a reduction in infant disease severity and hospitalization. Vaccine effectiveness was also reported to persist after the receipt of the first three DTaP doses, with immunization in pregnancy resulting in 70% lower risk of pertussis in vaccinated children whose mothers received Tdap in pregnancy.

Recommendations

Following the review of available evidence, NACI issued a recommendation for routine immunization with Tdap vaccine in every pregnancy. Complete details of the literature

review, rationale and relevant considerations for the updated recommendations can be found in the NACI Update on this topic (1) and the NACI Literature Review (2).

NACI recommends that immunization with Tdap vaccine should be offered in every pregnancy, irrespective of previous Tdap immunization history (Strong NACI Recommendation). NACI concludes that there is good evidence to recommend immunization (Grade A Evidence).

Routine maternal Tdap immunization during pregnancy will provide a more robust and complete protection against pertussis in infants compared to immunization during outbreak settings only. Tdap immunization in pregnancy has been shown to protect nine of 10 infants against pertussis younger than three months of age. No significant safety issues have been detected in the currently available body of scientific literature and no increased risk of serious adverse pregnancy, maternal or infant events have been reported in countries that are routinely offering Tdap vaccine for immunization in pregnancy. Similarly, no serious adverse events have been detected in Canada through Canadian Adverse Events Following Immunization Surveillance System (CAEFIS). There is currently no indication of a clinically significant change in the priming of the immunological memory of infants exposed to higher maternally-derived antibody concentrations following Tdap vaccination in pregnancy. Given the rapid waning of maternal antibody observed in studies, vaccination should be offered in each pregnancy irrespective of immunization history or the interval between pregnancies.

NACI recommends that immunization with Tdap vaccine should ideally be provided between 27 and 32 weeks of gestation (Strong NACI Recommendation, Grade A Evidence). Evidence also supports providing maternal Tdap over a wider range of gestational ages, and NACI recommends that it may be provided from 13 weeks up to the time of delivery in view of programmatic and unique patient considerations (Discretionary NACI Recommendation, Grade A/B Evidence).

Immunization should ideally be offered at 27–32 weeks of gestation, which is supported by the strongest safety and effectiveness data. Immunization between 13 and 26 weeks of gestation may also be considered in some situations (e.g., pregnancies with an increased risk of preterm delivery) to allow for longer placental exposure to higher antibody levels and maximization of antibody transfer. While it is preferable that immunization is administered in sufficient time before birth (i.e., four weeks) to allow optimal transfer of antibodies and direct protection of the infant against pertussis, it should be considered until the end of pregnancy in women who have not yet received it, as it has the potential to provide partial protection. If Tdap immunization was provided early in pregnancy (e.g., prior to recognition of pregnancy), it is not necessary to re-immunize after 13 weeks of gestation.

Various options for timing of pertussis immunization are possible; the decision on which option is preferable may depend on the considerations itemized in **Table 1**, below.

Table 1: Options and considerations for pertussis immunization during pregnancy

Options	Considerations	Decision points
1. Immunization at 27–32 weeks of gestation	Safety • Strong safety data in third trimester Effectiveness • Effectiveness data primarily span vaccination (27–36 weeks of gestation) Immunogenicity • Peak maternal anti-pertussis antibody levels are achieved approximately four weeks following vaccination • Placental transfer of maternal antibodies is optimal in third trimester Feasibility or acceptability • Could be paired with routine prenatal visit during which gestational diabetes screening is offered (24–28 weeks of gestation)	Optimal balance between safety data, clinical opportunities, limited antibody waning potential, efficient antibody formation and placental transfer for term pregnancies. This option is supported by the strongest safety and effectiveness data of all the options, and allows enough time for the antibody response to fully develop in pregnancy. Vaccination can be paired with routine maternal visits, but may not provide protection for some preterm births.
2. Immunization at 13–26 weeks of gestation	Safety • Fewer safety data in second trimester Effectiveness • Effectiveness data not stratified for immunization in second trimester (includes immunization in both second and third trimester) Immunogenicity • Peak maternal anti-pertussis antibody levels are achieved approximately four weeks following vaccination • Some reports have shown greater antibody concentrations in infants following vaccination at 13–25 weeks compared with that seen following vaccination at more than or equal to 26 weeks • Earlier vaccine administration in second trimester has been shown to result in higher antibody avidity (binding) Feasibility or acceptability • Could be paired with routine prenatal visits, either after detailed anatomical ultrasound is reviewed (typically done 18–22 weeks of gestation) or when gestational diabetes screening is performed (24– 28 weeks of gestation)	Safety data are fewer for second trimester, and effectiveness data are not stratified for immunization during second trimester. Second trimester vaccination increases clinical opportunities to offer vaccination and ensures optimal antibody formation and transfer for both term and preterm infants. For preterm deliveries, a narrow window of opportunity exists between onset of significant transplacental antibody transfer at 28 weeks and delivery.
3. Immunization before 13 weeks of gestation	Safety • Limited safety data in first trimester Effectiveness • No effectiveness data stratified for immunization prior to 13 weeks of gestation	Safety data are limited before 13 weeks, and effectiveness data are not stratified for first trimester immunization. When given early in pregnancy antibody may wane before term delivery.

Table 1: Options and considerations for pertussis immunization during pregnancy (cont'd)

Options	Considerations	Decision points
3. Immunization before 13 weeks of gestation (cont'd)	Immunogenicity • Maternal antibodies will start to wane prior to term delivery • Placental transfer of maternal antibodies is minimal prior to third trimester Feasibility or acceptability • If vaccine is administered prior to detailed anatomical ultrasound, fetal anomalies and other first trimester pregnancy-related complications may be misattributed to the vaccine • The vaccine may not be considered acceptable by patients and clinicians in the first trimester of pregnancy	There is a risk of adverse events in pregnancy being misattributed to vaccination.
4. Immunization after 32 weeks of gestation	Safety • Strong safety data in third trimester Effectiveness • Effectiveness data primarily span vaccination (27–36 weeks of gestation) Immunogenicity • Placental transfer of maternal antibodies is optimal in third trimester • Peak maternal anti-pertussis antibody levels are achieved approximately four weeks following vaccination Feasibility or acceptability • Clinical opportunities for vaccination exist with frequent routine prenatal visits towards the end of pregnancy	The strongest safety and effectiveness data are from the third trimester. This option may not allow sufficient time (i.e., four weeks) for the development and transfer of maternal antibodies before delivery. Late immunization will not provide protection for most preterm births. There may be fewer clinical opportunities to offer vaccination in late pregnancy compared with earlier vaccination.

Conclusion

There is now strong evidence to support the NACI recommendation that immunization with Tdap vaccine should be offered in every pregnancy. This is ideally administered between 27 and 32 weeks of gestation but evidence also supports providing maternal Tdap over a wider range of gestational ages from 13 weeks up to the time of delivery in view of programmatic and unique patient considerations.

Authors' statement

This statement was prepared by the NACI Pertussis Working Group: Dr. J. Brophy (Chair), Dr. N. Brousseau, Dr. E. Castillo, Dr. N. Crowcroft, Dr. S. Deeks, Dr. I. Gemmill, Dr. S. Halperin, Dr. B. Henry, Dr. M. Naus, Dr. M. Salvadori, Dr. B. Seifert.

Conflict of Interest

None.

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Rapid testing for TB drug-susceptibility

Source: Xie YL, Chakravorty S, Armstrong DT, Hall SL, Via LE1, Song T, Yuan X, Mo X, Zhu H, Xu P, Gao Q, Lee M, Lee J, Smith LE, Chen RY, Joh JS, Cho Y, Liu X, Ruan X, Liang L, Dharan N, Cho SN, Barry CE 3rd, Ellner JJ, Dorman SE, Alland D. **Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis**. N Engl J Med. 2017 Sep 14;377(11):1043-1054. http://dx.doi.org/10.1056/NEJMoa1614915.

Background: Fluoroquinolones and second-line injectable drugs are the backbone of treatment regimens for multidrug-resistant tuberculosis, and resistance to these drugs defines extensively drug-resistant tuberculosis. We assessed the accuracy of an automated, cartridge-based molecular assay for the detection, directly from sputum specimens, of *Mycobacterium tuberculosis* with resistance to fluoroquinolones, aminoglycosides, and isoniazid.

Methods: We conducted a prospective diagnostic accuracy study to compare the investigational assay against phenotypic drug-susceptibility testing and DNA sequencing among adults in China and South Korea who had symptoms of tuberculosis. The Xpert MTB/RIF assay and sputum culture were performed. *M. tuberculosis* isolates underwent phenotypic drug-susceptibility testing and DNA sequencing of the genes katG, gyrA, gyrB, and rrs and of the eis and inhA promoter regions.

Results: Among the 308 participants who were culture-positive for *M. tuberculosis*, when phenotypic drug-susceptibility testing was used as the reference standard, the sensitivities of the investigational assay for detecting resistance were 83.3% for isoniazid (95% confidence interval [CI], 77.1 to 88.5), 88.4% for ofloxacin (95% CI, 80.2 to 94.1), 87.6% for moxifloxacin at a critical concentration of 0.5 µg per milliliter (95% CI, 79.0 to 93.7), 96.2% for moxifloxacin at a critical concentration of 2.0 µg per milliliter (95% CI, 87.0 to 99.5), 71.4% for kanamycin (95% CI, 56.7 to 83.4), and 70.7% for amikacin (95% CI, 54.5 to 83.9). The specificity of the assay for the detection of phenotypic resistance was 94.3% or greater for all drugs except moxifloxacin at a critical concentration of 2.0 µg per milliliter (specificity, 84.0% [95% CI, 78.9 to 88.3]). When DNA sequencing was used as the reference standard, the sensitivities of the investigational assay for detecting mutations associated with resistance were 98.1% for isoniazid (95% CI, 94.4 to 99.6), 95.8% for fluoroquinolones (95% CI, 89.6 to 98.8), 92.7% for kanamycin (95% CI, 80.1 to 98.5), and 96.8% for amikacin (95% CI, 83.3 to 99.9), and the specificity for all drugs was 99.6% (95% CI, 97.9 to 100) or greater.

Conclusions: This investigational assay accurately detected *M. tuberculosis* mutations associated with resistance to isoniazid, fluoroquinolones, and aminoglycosides and holds promise as a rapid point-of-care test to guide therapeutic decisions for patients with tuberculosis. (Funded by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and the Ministry of Science and Technology of China; ClinicalTrials.gov number, NCT02251327).

Rapid diagnostic testing for TB meningitis

Source: Bahr NC, Nuwagira E, Evans EE, Cresswell FV, Bystrom PV, Byamukama A, Bridge SC, Bangdiwala AS, Meya DB, Denkinger CM, Muzoora C, Boulware DR; ASTRO-CM Trial Team. **Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study**. Lancet Infect Dis. 2018 Jan;18(1):68-75. https://dx.doi.org/10.1016/S1473-3099(17)30474-7. Epub 2017 Sep 14.

Background: WHO recommends Xpert MTB/RIF as initial diagnostic testing for tuberculous meningitis. However, diagnosis remains difficult, with Xpert sensitivity of about 50-70% and culture sensitivity of about 60%. We evaluated the diagnostic performance of the new Xpert MTB/RIF Ultra (Xpert Ultra) for tuberculous meningitis.

Methods: We prospectively obtained diagnostic cerebrospinal fluid (CSF) specimens during screening for a trial on the treatment of HIV-associated cryptococcal meningitis in Mbarara, Uganda. HIV-infected adults with suspected meningitis (eg, headache, nuchal rigidity, altered mental status) were screened consecutively at Mbarara Regional Referral Hospital. We centrifuged CSF, resuspended the pellet in 2 mL of CSF, and tested 0·5 mL with mycobacteria growth indicator tube culture, 1 mL with Xpert, and cryopreserved 0·5 mL, later tested with Xpert Ultra. We assessed diagnostic performance against uniform clinical case definition or a composite reference standard of any positive CSF tuberculous test.

Findings: From Feb 27, 2015, to Nov 7, 2016, we prospectively evaluated 129 HIV-infected adults with suspected meningitis for tuberculosis. 23 participants were classified as probable or definite tuberculous meningitis by uniform case definition, excluding Xpert Ultra results. Xpert Ultra sensitivity was 70% (95% CI 47-87; 16 of 23 cases) for probable or definite tuberculous meningitis compared with 43% (23-66; 10/23) for Xpert and 43% (23-66; 10/23) for culture. With composite standard, we detected tuberculous meningitis in 22 (17%) of 129 participants. Xpert Ultra had 95% sensitivity (95% CI 77-99; 21 of 22 cases) for tuberculous meningitis, which was higher than either Xpert (45% [24-68]; 10/22; p=0·0010) or culture (45% [24-68]; 10/22; p=0·0034). Of 21 participants positive by Xpert Ultra, 13 were positive by culture, Xpert, or both, and eight were only positive by Xpert Ultra. Of those eight, three were categorised as probable tuberculous meningitis, three as possible tuberculous meningitis, and two as not tuberculous meningitis. Testing 6 mL or more of CSF was associated with more frequent detection of tuberculosis than with less than 6 mL (26% vs 7%; p=0·014).

Interpretation: Xpert Ultra detected significantly more tuberculous meningitis than did either Xpert or culture. WHO now recommends the use of Xpert Ultra as the initial diagnostic test for suspected tuberculous meningitis. (Funding: National Institute of Neurologic Diseases and Stroke, Fogarty International Center, National Institute of Allergy and Infectious Disease, UK Medical Research Council/DfID/Wellcome Trust Global Health Trials, Doris Duke Charitable Foundation).

Authors' correction: Can Commun Dis Rep. 2018;44(2)

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Suggested citation: Canada Communicable Disease Report Editorial Team. Authors' correction: Can Commun Dis Rep. 2018;44(2). Can Commun Dis Rep. 2018;44(3/4):96.

In the article "Outbreak of Seoul virus among rats and rat owners — United States and Canada, 2017" (1) the following correction was made on March 1, 2018 upon the request of the authors.

In the section titled "Public Health response", the date in the second sentence of the first paragraph was corrected as follows:

On February 10, 2017, the World Health Organization was notified of the US and Canadian infections and investigations as required by International Health Regulations.

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1. Kerins JL, Koske SE, Kazmierczak J, Austin C, Gowdy K, Dibernardo A, Seoul Virus Working Group, Canadian Seoul Virus Investigation Group (Federal), Canadian Seoul Virus Investigation Group (Provincial). Outbreak of Seoul virus among rats and rat owners — United States and Canada, 2017. Can Dis Commun Rep. 2018;44(2): 71-4. https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-2-february-1-2018/article-7-seoul-virus-outbreak-2017.htm

Errata: Can Commun Dis Rep 2017;43(12)

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In the Web Exclusive of the December 2017 issue of Canada Communicable Disease Report (CCDR):

HIV in Canada – Supplementary tables, 2016 (1)
AIDS in Canada – Supplementary tables, 2016 (2)

the suggested citations were missing. These were added on March 1, 2018. No changes were needed for the pdf version of the issue.

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1. AC Bourgeois, M Edmunds, A Awan, L Jonah, O Varsaneux, W Siu. HIV in Canada – Supplementary tables, 2016. Can Commun Dis Rep. 2017;43(12): https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2017-43/ccdr-volume-43-12-december-7-2017/hiv-2016-supplementary-tables.html
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Erratum: Can Commun Dis Rep 2017;43(11)

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Tuberculosis drug resistance in Canada: 2006–2016 Supplementary data (1)

the suggested citation was missing. It was added on March 1, 2018. No changes were needed for the pdf version of the issue.

Reference

1. V Gallant, J Vachon, W Siu. Tuberculosis drug resistance in Canada: 2006–2016 Supplementary data. Can Commun Dis Rep. 2017;43(11): https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2017-43/ccdr-volume-43-11-november-2-2017/tuberculosis-drug-resistance-canada-2006-2016-supplementary-data.html

Erratum: Can Commun Dis Rep 2017;43(3/4)

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In the Web Exclusive of the March 2017 issue of Canada Communicable Disease Report (CCDR):

Tuberculosis in Canada: 2015 Supplementary data (1)

the suggested citation was missing. It was added on March 1, 2018. No changes were needed for the pdf version of the issue.

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1. V Gallant, V Duvvuri, M McGuire. Tuberculosis in Canada: 2015 Supplementary data. Can Commun Dis Rep. 2017;43(3/4). https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2017-43/ccdr-volume-43-3-4-march-2-2017/ccdr-volume-43-3-4-march-2-2017-tuberculosis-4.html

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