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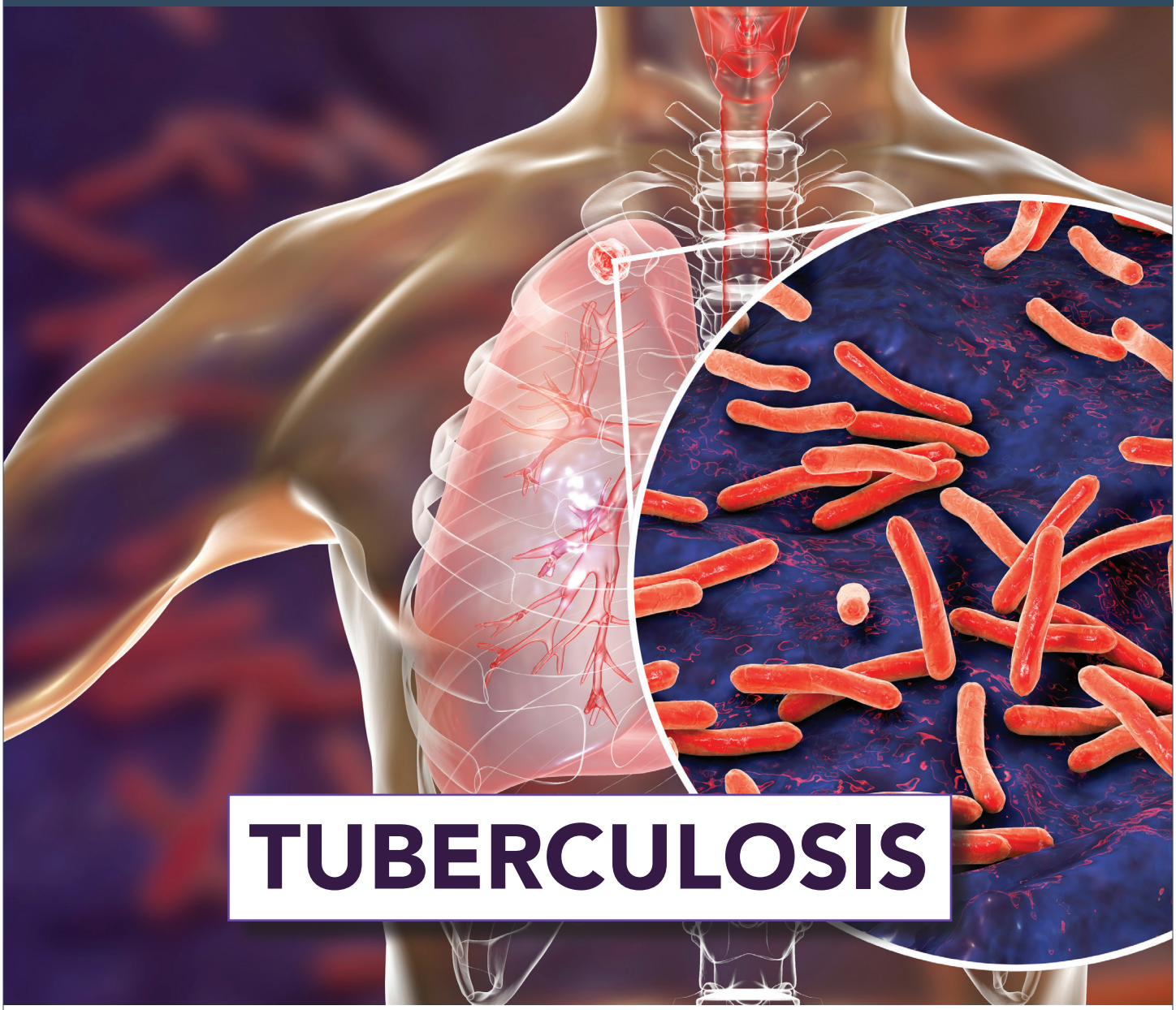

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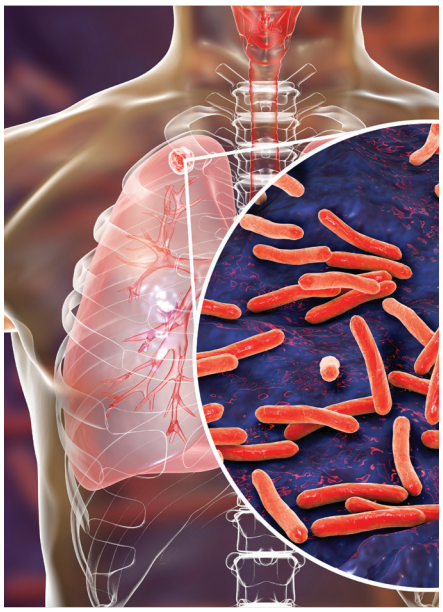

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Summary of the National Advisory Committee on Immunization (NACI) Statement: Updated guidance on human papillomavirus (HPV) vaccines

Nicole Forbes[1], Josh Montroy[1], Marina I Salvadori[1,2], Vinita Dubey[3] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Without vaccination, approximately 75% of people in Canada will acquire a human papillomavirus (HPV) infection in their lifetime. HPV vaccine coverage rates continue to fall short of the national goal of 90% coverage for two or more doses by 17 years of age. Recent evidence and World Health Organization (WHO) guidance now support a 1- or 2-dose schedule for younger age groups, which can simplify vaccination efforts and improve coverage rates compared to a multi-dose immunization program.

Methods: The National Advisory Committee on Immunization (NACI) reviewed available evidence on the clinical benefits and risks of a 1-dose HPV vaccine schedule, as well as additional factors, including ethics, equity, feasibility and acceptability. The evidence and programmatic considerations were organized using a process informed by the Grading of Recommendations Assessment, Development and Evaluations (GRADE) framework and all of the information was used to facilitate NACI guidance development.

Results: A 1-dose schedule is highly effective against HPV infection based on available evidence in younger female populations, with current follow-up of up to 11 years following vaccination. Infectious disease modelling shows that a 1-dose strategy in males and females in Canada is expected to have similar health outcomes over the short and long term compared to two doses.

Conclusion: NACI updated recommendations for individuals 9 to 20 years of age to receive one dose of 9vHPV (Gardasil-9, Merck) vaccine. For individuals 21 years of age and older, a 2-dose schedule should be administered. Individuals considered immunocompromised and individuals infected with HIV should receive a 3-dose series. NACI also issued a discretionary recommendation for HPV vaccination for individuals 27 years and older, and updated guidance to allow HPV vaccine during pregnancy.

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Introduction

Human papillomavirus (HPV)-associated diseases pose a substantial public health challenge globally and in Canada. HPV infection is highly prevalent, with an estimated 75% of individuals experiencing at least one infection in their lifetime if unvaccinated (1). HPV-associated diseases include cervical, anal, and oropharyngeal cancers, as well as anogenital warts and recurrent respiratory papillomatosis, a rare but serious disease.

In Canada, HPV vaccination is a cornerstone of public health efforts to prevent HPV-related diseases. The Canadian HPV Immunization Program aims to reduce HPV-associated morbidity and mortality by ensuring universal access to vaccines (2) and the current national goal is to achieve 90% vaccine coverage of 2 doses or more by 17 years of age (3). The goal aligns with HPV vaccination goals set forth in the Canadian Partnership Against Cancer Action Plan for the Elimination of Cervical Cancer in Canada (4). However, vaccination rates vary across provinces, with many jurisdictions falling well below the 90% goal (5)

The National Advisory Committee on Immunization (NACI) last updated its recommendations in 2017, recommending 2- or 3-dose schedules depending on age and immune status. Recent evidence and World Health Organization (WHO) guidance now support a 1- or 2-dose schedule for younger age groups, which is expected to potentially simplify vaccination efforts and improve coverage rates compared to a multi-dose immunization program. According to the WHO 2022 guidance, a single-dose schedule, referred to as an alternative, off-label single-dose schedule, can provide comparable efficacy and durability of protection to a 2-dose regimen for individuals aged 9 to 20 years (6).

NACI has since reviewed evidence and provided guidance on the recommended use of HPV vaccines, and updated recommendations on HPV vaccine schedules (5). A summary of updated NACI guidance on HPV vaccines follows.

Methods

For this interim guidance, NACI reviewed key questions as proposed by the NACI HPV Working Group, including those on HPV vaccine schedule by population and on HPV vaccine guidance during pregnancy. Evidence synthesis was performed by the NACI Secretariat and reviewed by the NACI HPV Working Group. Following critical appraisal of individual studies, summary tables with ratings of risk of bias informed by Cochrane RoB 2 and ROBINS-I, as appropriate, were prepared (7). The evidence and programmatic considerations were organized by the NACI Secretariat using a process informed by the Grading of Recommendations Assessment, Development and Evaluations (GRADE) framework and all of the information was used to facilitate development of NACI guidance.

NACI uses a published, peer-reviewed framework and evidence-informed methodology to ensure that issues related to ethics, equity, feasibility and acceptability are systematically assessed and integrated into the guidance (8). NACI considered feedback provided by the Public Health Ethics Consultative Group, the Canadian Immunization Committee and the Public Health Agency of Canada. Further information on NACI's evidence-based methods is available in *Evidence-based recommendations for immunization - Methods of the National Advisory Committee on Immunization*.

To inform policy recommendations in Canada, mathematical modelling was used to project the population-level impact and efficiency of switching from 2-dose to 1-dose gender-neutral routine HPV vaccination (9). Using the previously validated HPV-ADVISE model, an individual-based transmission-dynamic model of HPV infection and disease, two provinces (Québec and Ontario) were modelled; these two provinces represented higher (≈85%) and lower (≈65%) HPV vaccination coverage in Canada, respectively. Non-inferior and pessimistic scenarios of 1-dose efficacy (vaccine efficacy=98%, 90%) and average duration of protection (duration of vaccine protection=lifelong, 30 years, 25 years) were compared to two doses (vaccine efficacy=98%, duration of vaccine protection=lifelong). The main outcomes were incidence of HPV-16 infections (among females and males), cervical cancer and other HPV-associated cancers and the number needed to vaccinate to prevent one case of cervical cancer.

NACI reviewed available evidence and approved updated guidance on May 27, 2024.

Results

Efficacy and effectiveness of a 1-dose HPV vaccine schedule compared to no HPV vaccine

Compared to no HPV vaccine, the available evidence from randomized controlled trials demonstrated that a 1-dose HPV vaccine schedule resulted in a large reduction in persistent HPV infections with product-specific vaccine types, through three years following vaccination (high certainty of evidence) (10). Evidence from non-randomized trials demonstrated similar effects, with a single dose of HPV vaccine resulting in reductions of persistent, incident and prevalent HPV infections with product-specific vaccine types, compared to no vaccine (moderate certainty of evidence; follow-up ranging from 6 to 11 years) (11–14), as well as reductions in anogenital warts (moderate certainty of evidence; follow-up of approximately 2.5 years) (15).

Efficacy and effectiveness of a 1-dose HPV vaccine schedule compared to a 2- or 3-dose HPV vaccine schedule

Compared to a 2- or 3-dose schedule, available evidence suggests that a 1-dose schedule may provide similar protection from HPV infection with product-specific vaccine types, through 11 years following vaccination. Compared to two or three doses, there may be little to no difference in the risk of persistent, incident or prevalent HPV infections with product-specific vaccine types (low certainty of evidence, follow-up ranging from 4 to 11 years) (11–13), or in the risk of anogenital warts (low certainty of evidence; follow-up of approximately 2.5 years), with a 1-dose HPV vaccine schedule (15). Similarly, there may be little to no difference in the risks of cervical abnormalities or cervical intraepithelial neoplasia grade 2+ (CIN2+) between 1-dose and either 2- or 3-dose schedules (low certainty of evidence; follow-up of 10 years), although evidence is currently limited (12).

Immunogenicity

Numerous clinical trials have demonstrated a 1-dose, 2-dose or 3-dose HPV vaccine series generates a robust immunological response to HPV vaccine antigens. While a 2- or 3-dose schedule results in significantly higher antibody titers than a 1-dose schedule, the response generated by a 1-dose, 2-dose or 3-dose HPV vaccine schedule first peaks, then remains relatively stable, out to 16 years. Compared to natural infection, a single dose results in significantly higher antibody titres, out to at least 10 years (16,17). Currently, there is no established correlate of protection for HPV, and therefore the clinical relevance of differences in the immune response following different HPV vaccine schedules is unknown (17–19).

Vaccine safety

According to 9vHPV clinical trial data, the most common injection-site reactions following vaccination in those 9 to 26 years of age were pain, swelling, and redness. The most common systemic reactions included headache and fever (37.8°C or greater) for both sexes, as well as nausea for females. Female participants reported higher frequency of adverse events following the third dose of 9vHPV compared to the first two doses for all outcomes, except any pain, which was highest following the second dose in females aged 16 to 26 years (20). For males, injection site adverse events were generally similar after the first, second and third doses; however, the frequency of vaccine-related systemic events was highest following the first dose and decreased following subsequent doses (21). Additionally, no safety concerns associated with the 9vHPV vaccine have been identified with the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) from product licensure date to time of NACI guidance deliberations.

Regarding 9vHPV vaccine safety during pregnancy, available data indicate no increased risk of adverse pregnancy outcomes associated with 9vHPV during or around pregnancy, and any adverse outcomes appear to occur at similar rates as observed in the general population (22), which is consistent with the safety profile for 2vHPV (bivalent HPV vaccine; Cervarix, Glaxo-Smith-Kline) and 4vHPV (quadrivalent HPV vaccine; Gardasil-4, Merck) vaccines when administered during pregnancy (23).

Disease modelling

Canadian-specific disease modelling estimates that 1-dose HPV vaccination would avert a number of HPV-associated cancers that is similar to two doses in Canada, under various modelling scenarios (9). Additionally, all 1-dose strategies were projected to lead to cervical cancer elimination (fewer than four cases per 100,000 woman years) within 15 to 25 years and were projected to be a substantially more efficient use of vaccine doses compared to two doses (number needed to vaccinate for 1-dose vs. no vaccination: 768 to 1,012 individuals; incremental number needed to vaccinate for 2-dose vs. 1-dose vaccination: >10,000 individuals). Switching to a 1-dose program nationally would still produce gains despite varying vaccination coverage among provinces. If 1-dose protection is shown to wane substantially in the next 10 years, modelling showed that switching back to 2-dose routine vaccination of adolescents after 10 years of 1-dose vaccination could mitigate losses in HPV-associated cancer prevention, leading to similar numbers of cancers averted as would be the case in remaining with 2-dose vaccination (catch-up vaccination with a second dose would not be required) (9). Additional work is required to better understand the progression rate and dynamics for other HPV-associated cancers and among equity-deprived populations.

Ethics and equity considerations

Following implementation of a 1-dose HPV immunization program, it will be essential to maintain immunization opportunities to prevent lower vaccination rates among vulnerable communities already facing disparities in HPV-associated diseases. Specifically, First Nations, Métis and Inuit populations in Canada experience higher rates of HPV infection and associated disease, as well as lower cervical cancer screening rates, which can be complicated by stigmatization and discrimination when accessing healthcare (24). Of note, recent Canadian data reports that Indigenous women are two to 20 times more likely to be diagnosed with cervical cancer compared to non-Indigenous women and have a mortality rate from cervical cancer four times higher than non-Indigenous women (25–28). Immigrant and refugee populations also face increased HPV-related risks and are reported to have lower cervical cancer screening rates (29). Addressing socio-demographic disparities in vaccination rates will be integral for equitable HPV immunization policy and may require enhanced access and uptake strategies tailored to equity-denied groups. These may include catch-up programs, expanded vaccine access in primary healthcare delivery and in schools, simplified consent processes and targeted resource allocation to equity-denied groups.

NACI recommendations on HPV vaccines for public health program-level decision-making

The following are recommendations for provinces/territories making decisions for publicly funded immunization programs:

- NACI continues to recommend HPV vaccination for all individuals 9 to 26 years of age. (***Strong NACI recommendation)***
- NACI recommends that individuals 9 to 20 years of age should receive one dose of HPV vaccine, and individuals 21 to 26 years of age should receive two doses of HPV vaccine. (***Strong NACI recommendation***)
- Nonavalent 9vHPV vaccine should be used, as it provides protection against the greatest number of HPV types and associated diseases. (***Strong NACI recommendation***)

Recommendations for individual-level decision-making

The following recommendation is for healthcare providers advising individual clients:

- Individuals 27 years of age and older may receive the HPV vaccine with shared decision-making and discussion with a healthcare provider. The vaccine should be given as a 2-dose schedule with doses administered at least 24 weeks apart. (***Discretionary NACI recommendation***)

Additional guidance on HPV vaccines

Additional guidance on HPV vaccines includes the following:

- A 2-dose schedule may be considered on an individual basis for individuals 9 to 20 years of age with their healthcare provider. When two doses are offered, doses should be administered at least 24 weeks apart.
- HPV vaccines can be offered in pregnancy; routine questioning about last menstrual period or pregnancy is not required or recommended before offering the HPV vaccine. The rationale for this is as follows:
    - HPV infection during pregnancy may lead to adverse outcomes to the pregnant woman or pregnant individual and to the fetus.
    - The HPV vaccine is expected to provide a benefit to anyone who is at ongoing risk of HPV infection, including during pregnancy.
    - Evidence to date demonstrates no increased risk of adverse pregnancy or fetal outcomes associated with HPV vaccination during pregnancy. There is no known evidence nor biological mechanism to expect an increased risk of adverse pregnancy or fetal outcomes with HPV vaccination during pregnancy.
- NACI reiterates its current guidance on a 3-dose schedule for individuals who are considered immunocompromised, as well as individuals living with HIV, when recommended to receive HPV vaccination. See the *Canadian Immunization Guide* for additional guidance.
- NACI emphasizes the ongoing need for additional public health measures, such as HPV infection and associated cancer screening and surveillance and early access to treatment to prevent HPV-associated diseases for all Canadians. Trends in HPV infection incidence or the incidence of HPV-associated outcomes will be important to monitor in relation to any changes to HPV vaccine immunization programs.
- NACI also encourages dedicated efforts to implement such measures to equity-denied groups, including First Nations, Inuit and Métis people, some of whom face disproportionately high rates of HPV-associated cancers and lower rates of HPV immunization. Continuing to provide HPV vaccination in school-based programs has been shown to reduce health inequities.

Given ongoing efforts to improve HPV vaccination coverage and reduce HPV-associated burden of disease among people in Canada, and considering recent updated guidance from the WHO, NACI used an evidence-informed approach to update guidance on HPV vaccine schedules. NACI guidance on recommended schedules for HPV vaccines is summarized below in **Table 1**. Updated NACI guidance now includes recommendations on the use of the 9vHPV vaccine to provide protection from the greatest number of vaccine-preventable strains. NACI also issued a discretionary recommendation for HPV vaccination for individuals 27 years and older, and updated guidance to allow HPV vaccine during pregnancy.

Table 1: NACI recommendations on HPV immunization schedules

Group(s)	NACI guidelines on HPV immunization schedules
9–20 years[a]	1-dose[b] HPV vaccine schedule with 9vHPV
21–26 years[a]	2-dose HPV vaccine schedule with 9vHPV; doses administered at least 24 weeks apart
27 years and older[a]	2-dose HPV vaccine schedule with 9vHPV; doses administered at least 24 weeks apart
9 years and older[a] who are immunocompromised or living with HIV	3-dose HPV vaccine schedule[c] with 9vHPV

Abbreviations: HPV, human papillomavirus; NACI, National Advisory Committee on Immunization
[a] Recommended schedule is based on age at initiation of vaccination
[b] A 2-dose schedule may be considered on an individual basis for individuals 9–20 years of age. When two doses are offered, doses should be administered at least 24 weeks apart
[c] Individuals recommended to receive HPV vaccine who are immunocompromised, including individuals living with HIV, should receive a 3-dose HPV vaccine schedule with a nonavalent HPV vaccine. The minimum interval between the first and second doses of vaccine is four weeks (one month), the minimum interval between the second and third doses of vaccine is 12 weeks (three months) and the minimum interval between the first and last doses is 24 weeks (six months)
Note: Refer to the *Human papillomavirus (HPV) vaccines: Canadian Immunization Guide* chapter in Part 4 for additional guidance on recommended HPV vaccine schedules

Conclusion

NACI will continue to monitor evidence of 1-dose HPV vaccine schedules, including long-term durability (e.g., 20+ years follow-up time) and clinical outcomes. As evidence becomes available from clinical trials, Canadian data and other countries where similar schedules are adopted, NACI will issue updates to guidance as warranted. To maximize the benefits of a reduced dose schedule, Canadian jurisdictions that adopt 1-dose HPV immunization programs should aim to increase coverage and maintain immunization opportunities among those at risk, especially among vulnerable communities already facing disparities in HPV-associated diseases.

Authors' statement

NF — Writing–original draft, writing–review & editing
JM — Writing–review & editing
MIS — Writing–review & editing
VD — Writing–review & editing

The *NACI Statement: Updated recommendations on human papillomavirus vaccines* was prepared by N Forbes, V Dubey, J Montroy, K Gusic, M Salvadori, A Howarth, A Tuite, R Harrison and M Tunis, on behalf of the NACI HPV Working Group, and was approved by NACI.

Competing interests

None.

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Popularity of HIV self-tests may say more about the state of our primary care system than about the device itself

Alexandra Musten[1]*, Patrick O'Byrne[1]

Abstract

Background: In Canada, HIV transmission continues to disproportionately affect the same communities of gay men, bisexual men and men who have sex with men (gbMSM); members of African, Caribbean or Black communities (ACB); people who use injection drugs; Indigenous people; and women who belong to the aforementioned groups. While primary care is an ideal location for HIV testing for members of these groups, many people do not have access to such healthcare services. In response, we launched GetaKit to distribute HIV self-tests.

Methods: In light of reduced access to healthcare services as a result of the pandemic and in anticipation of Health Canada's approval of an HIV self-test, a clinician-scientist research team at the University of Ottawa developed GetaKit: an online platform to provide access to sexual health services. When GetaKit first launched in Ottawa in July 2020 with funding from the Ontario Ministry of Health, its objectives were to ensure that access to the newly approved device remained 1) clinically appropriate, 2) accessible and 3) linked to care.

Results: Over the course of the study, there were a stable number of individuals who reported having never been tested for HIV before. These individuals tended to be younger and more likely to be members of racialized minority groups; similar characteristics to those who also face the most barriers to primary care access.

Conclusion: With new reports indicating that nearly six million Canadians are without a primary care provider, it was proposed that the popularity of the HIV self-test may tell more about this lack of access than about the utility of the device itself. While projects like GetaKit should be part of the broader strategy to overcome historic testing barriers, such as geographic distance and inconvenient clinic hours, it is important that this occurs in an environment where a strong primary care health system can support treatment, follow-up and specialist referrals, as required.

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Introduction

In Canada, primary care is often an individual's first interaction with the healthcare system and is considered a basic tenet of universal health coverage (1). Yet, there are individuals in Ontario who are not connected with a primary care provider, resulting in unmet healthcare needs and worsened health outcomes (2). Moreover, during the COVID-19 pandemic, nearly 170,000 people in Ontario lost access to their primary care providers due to burnout and retirements (3). This is of particular concern with respect to HIV testing because, in Ontario, most HIV tests are ordered by primary care providers. The result of the foregoing situation is that, in 2020, HIV testing decreased by 56% in sexual health clinics, 42.8% in community health centres and 31.1% in other clinic settings (4).

Of further concern is that there is considerable overlap between the individuals who experience reduced access to primary care and the groups who are most affected by HIV in Ontario, including gay men, bisexual men and men who have sex with men (gbMSM); members of African, Caribbean or Black communities (ACB); people who use injection drugs; Indigenous people; and women who belong to the aforementioned groups (2). A randomized controlled trial performed in Ontario in 2021 found that physicians who had been practising over 20 years were nearly 13 times less likely to take on a patient who disclosed having an opioid use disorder (5). Black people also continue to be disproportionately affected by social and health inequities, including poor access to healthcare, and experience worse health outcomes (6). Another study reviewing hospitalization rates among Ontario's Indigenous communities found that their higher rate of hospitalization compared to the general population is indicative of insufficient or ineffective primary care (7). In a setting where primary care is responsible for the delivery of prevention services and management of chronic diseases, and is a referral source to specialists, it is unacceptable that groups continue to experience vulnerability due to their sometimes deliberate exclusion from basic care (7).

Methods

In light of reduced access to healthcare services as a result of the pandemic and in anticipation of Health Canada's approval of an HIV self-test, a clinician-scientist research team at the University of Ottawa developed GetaKit: an online platform to provide access to sexual health services. When GetaKit first launched in Ottawa in July 2020 with funding from the Ontario Ministry of Health, its objectives were to ensure that access to the newly approved device remained 1) clinically appropriate, 2) accessible and 3) linked to care. Individuals who wished to obtain an HIV self-test were invited to review and accept the study consent form, create their account and complete the self-assessment questionnaire at GetaKit.ca. If testing was recommended, an HIV self-test was shipped to their address with linkage to care information. Participants were sent email reminders to submit their results by logging into their GetaKit.ca account. Individuals who submitted an invalid result were given a new test, individuals who submitted a negative result were sent a retest reminder three months later and those who submitted a positive result were provided support and then directly linked to confirmatory testing and care.

Results

During the first six months of launching GetaKit.ca, 1,268 individuals visited the website and 47.3% (n=600) were eligible to receive a free HIV self-test. Of the 399 individuals who were eligible and completed the assessment, 71% (n=283) reported belonging to at least one of the groups that are most affected by HIV in Ontario, 24% reported no prior HIV testing and 33% (n=128) indicated that they did not have a primary care provider. For those who reported prior HIV testing, 55% (n=154) had been tested in a public health clinic and 34% had tested with a primary care provider. Interestingly, individuals who reported not being a member of the groups most affected by HIV in Ontario were nearly five times more likely to have been tested by a primary care provider compared to a public health clinic, underscoring access barriers among equity-deserving groups (8).

Since the first phase of GetaKit.ca, this service is now available across Ontario and, to date, has offered testing to over 17,000 people. Of these, 65% were cisgender male, 26% were cisgender female, 51% identified as gbMSM and 32% as heterosexual. Notably, 18% of GetaKit.ca participants identified as ACB, when ACB persons only make up 4% of Ontario's population (9). GetaKit has furthermore identified 32 new HIV diagnoses since 2020, all of whom have completed confirmatory bloodwork and have been linked to care in their area. Over the course of the project, another observation is that a sizeable and stable number of participants (~30%) reported that this was their first time testing for HIV; an important indicator of success, as it demonstrates engagement with individuals who may not have accessed testing otherwise. First-time testers accessing GetaKit tended to be younger and more likely to be members of racialized minority populations (10).

Discussion

This finding is not surprising. After all, excitement around the approval of the HIV self-test was deeply rooted in its promise to aid individuals in overcoming historic barriers to testing (11). These include, but are not limited to, geographic distance, conflicting hours of operation and experiences of racism, transphobia, homophobia, stigma and/or other forms of discrimination in healthcare (12). Recent reports indicate that more than six million Canadians say that they do not have regular access to a primary care provider (13). This threatens to place undue stress on other services. A survey completed in 2020 found that 39% of Canadians visited an emergency department for an issue that could have been treated by a primary care provider (14). One such item that people have been seeking through emergency departments includes testing for sexual transmitted infections and HIV (15). It is within this environment that the uptake of, and the demographics of individuals ordering, HIV self-tests should be contextualized. Given historical barriers to services, compounded by the pandemic, the popularity of the HIV self-test may say more about the state of our primary care system than it does about the usefulness of the device itself. In other words, people were excited for HIV self-testing not because this was necessarily how they wanted to do HIV testing; rather, they simply wanted access to such testing (which was otherwise difficult for them to obtain).

In 2023, GetaKit.ca expanded its testing options to include testing for other sexually transmitted and blood-borne infections (STBBIs). Working in close partnership with public health units in Ontario, GetaKit.ca now offers testing for gonorrhea, chlamydia, syphilis, hepatitis C and HIV serology to participants who, in alignment with current clinical guidelines, meet the criteria for testing. If a participant lives in an area where full STBBI testing is available, they will be prompted to select the tests they would like to receive. Early findings indicate that while the number of orders that are being processed through the GetaKit.ca platform have increased over tenfold since STBBI testing became available (which has resulted in HIV testing nearly tripling), the demand for the HIV self-test has decreased. In other words, when other tests (including the option of serological testing for HIV) become readily available, participants not only choose full testing, but they also opt for serology over the HIV self-test. Perhaps it is unsurprising that, when given the option, people select the higher quality healthcare service.

In all cases, these findings are encouraging, indicating that GetaKit.ca can provide additional services to bridge the gap in testing created in the wake of the pandemic. For individuals, this means providing an easy and convenient access point for routine testers, as well as providing an option for others who may be unable or unwilling to attend an in-person appointment. For sexual health clinics, this means reducing pressure on already tight resources in a sector that has yet to fully recover from the impact of COVID-19 (16).

Limitations

The success of GetaKit.ca comes with caveats. While the availability of STBBI testing through GetaKit.ca absolutely provides an opportunity to lessen the stress on brick-and-mortar clinics, redirects routine procedures to self-collection methods and offers judgment-free services, it should not be forgotten that these are necessary because our healthcare system is unable to meet the current demand for care. Again, the success of GetaKit.ca may speak more to the state of our healthcare system, rather than to the platform being ideal. There are other limitations that must be acknowledged; for example, the individuals who can access testing through digital platforms represent a subset of the at-risk populations who are able to overcome different barriers, such as digital and health literacy, access to stable internet and a fixed address for shipping. Moreover, results that necessitate follow-up testing, repeat testing or treatment still require that individuals interact with the healthcare system in its current state and there remain some communities who are unable or unwilling to do this. For some, this may mean reintroducing the original barriers, such as geographical distance, inconvenient hours of operation and experiences of racism and discrimination. We must therefore exercise caution when discussing the benefits of HIV self-testing, which is predominantly available online, lest those who are unable to navigate access (i.e., due to low digital literacy, limited access to stable internet, no fixed address) and have limited linkage to care pathways are left with fewer or no options for testing. Finally, at the time of writing, there exists no permanent public source of funding for HIV self-test distribution, which calls into question its long-term availability.

Conclusion

Projects like GetaKit.ca, which offer health services in alignment with clinical guidelines with a focus on strong linkage to care pathways, can likely bridge a major gap in access to HIV testing (and to broader STI testing) for many. Participant preference for HIV serology over the HIV self-test when given the choice indicates that it is access to healthcare services, not to any one device, that attracts people. The success and sustainability of new testing devices and digital health services depend on strong primary care services to fulfill their mandate in offering high quality, low barrier healthcare for everyone. This means, as we continue to improve access to STBBI testing, we must also invest in our primary care system to enable providers to support new diagnoses identified through projects like GetaKit.ca and provide judgment-free care to individuals with complex care needs.

Authors' statement

AM — Conceptualization, writing–original draft, writing–review & editing
PB — Writing–review & editing

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

None.

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Mycobacterium tuberculosis pseudo-outbreak due to laboratory cross-contamination: A molecular epidemiology outbreak investigation

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Abstract

Background: Mycobacterial culture is routinely performed to diagnose tuberculosis (TB) in Canada. Globally, meta-analyses suggest that up to 2% of positive cultures are falsely positive for *Mycobacterium tuberculosis* due to laboratory cross-contamination. Five patients from distinct clinical institutions in Montréal were diagnosed with culture-positive TB as their clinical samples were processed in a centralized mycobacteria laboratory. Cross-contamination was suspected due to culture positivity in an organ donor with low TB pre-test probability. We describe a TB pseudo-outbreak due to laboratory cross-contamination and assess the role of conventional typing (i.e., mycobacterial interspersed repetitive unit variable number of tandem repeats [MIRU-VNTR]) and whole-genome sequencing (WGS) in supporting the investigation.

Methods: Patients' epidemiological risk factors and clinical presentations were reviewed. The trajectories of pre- and per-analytic samples were retraced to identify potential cross-contamination events. Tuberculosis isolates were characterized by MIRU-VNTR and WGS using Oxford Nanopore Technology (ONT). The bioinformatic pipeline tbpore (v0.7.1) cluster was used for phylogenetic analyses.

Results: Two patients had previous exposure to endemic settings and clinical symptoms compatible with TB. Culture media inoculation overlapped in time for four patients, including one with suspected pulmonary cavitary disease and an organ donor whose organs had been transplanted in three different receivers. The MIRU-VNTR and WGS typing confirmed isolates from those four patients to be identical.

Conclusion: Clinical, laboratory and molecular typing data, including results from ONT sequencing, were considered sufficiently robust to confirm laboratory cross-contamination and TB therapy was discontinued including in all organ transplant recipients.

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Introduction

According to the Public Health Agency of Canada (PHAC), 1,971 cases of active tuberculosis (TB) were reported in 2022, with an associated incidence of 5.1 TB cases per 100,000 people, which has been stable in the last 20 years (1,2). In every Canadian province and territory, TB is a mandatory reportable disease and mandatory treatment is enforced by public health authorities in cases of contagious respiratory active disease (3,4). Laboratory diagnosis of TB, therefore, has significant clinical and public health implications.

Laboratory cross-contamination was previously reported as a cause of false positive *Mycobacterium tuberculosis* culture. A systematic review published in 2019, including 31 articles regrouping 29,839 TB cultures, suggested that 2% of positive culture results were false positives. For positive cultures from patients with a prior negative sample or negative follow-up sample, the rate of false positives was increased to 15% (5). Contamination events are increasingly reported due to wider availability of bacterial genotyping which facilitates the investigation of contamination events (6). Similarly for person-to-person transmission and outbreak investigations, restriction fragment length polymorphism (RFLP) and mycobacterial interspersed repetitive unit variable number of tandem repeats (MIRU-VNRT) methods are increasingly replaced by higher resolution whole-genome sequencing (WGS) as the method of choice for molecular genotyping (6–10).

We report on a *M. tuberculosis* laboratory contamination event and pseudo-outbreak that has had significant clinical and public health impacts, including among organ transplant patients. We detail our epidemiology and molecular investigation approach, which included patients' clinical assessments and bacterial DNA sequencing using the Oxford Nanopore Technologies (ONT) next-generation sequencing (NGS) platform and publicly available adapted bioinformatic analysis tool, tbpore cluster (version 0.7.1) (11). Ways to further mitigate the risk of future contamination events are also proposed.

Results

Setting and participants

The *Centre hospitalier de l'Université de Montréal* (CHUM) is a 700-bed quaternary care hospital providing care to specific populations at higher risk of mycobacterial infections, including cystic fibrosis, lung and other organ transplants, and oncology patients. Our Biosafety Level 3 clinical mycobacteria laboratory processes thousands of samples every year and performs mycobacterial smear microscopy, culture and nucleic acid amplification testing (NAAT) for species of the *M. tuberculosis* complex. All positive cultures are referred to our provincial reference laboratory (*Laboratoire de santé publique du Québec*, LSPQ), where sequencing-based speciation and phenotypic drug susceptibility testing is performed, if indicated.

Investigation

A false positive *M. tuberculosis* culture result was initially suspected by a clinical infectious disease physician from CHUM in 2023. The positive sample had been collected during lung harvesting from a deceased organ donor. Such cultures are routinely performed to establish pre-transplant donor organ colonization and guide post-transplant receiver empiric antimicrobial therapy. This organ donor had been clinically screened, and in the absence of epidemiological risk factors, was considered to have a null pre-test probability for TB. Tuberculosis infection screening with either tuberculin skin test or interferon-gamma release assay (IGRA) is not routinely performed among organ donors because of low TB incidence in Québec organ donors. The 48-hour minimum assay turnaround time is also frequently too long in the context of urgent post-mortem organ harvesting. This single donor was involved in pulmonary, cardiac, and renal transplantations to three distinct patients receiving post-transplant medical care in three different institutions.

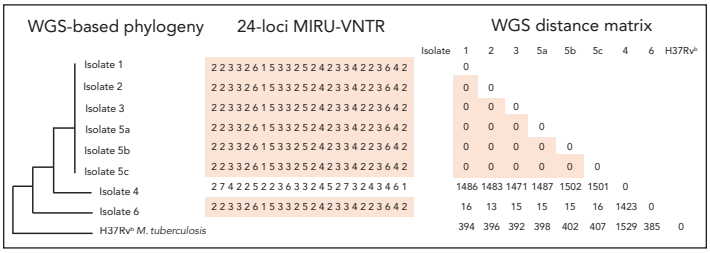
Following clinical suspicion of a false positive result, laboratory, clinical and public health investigations were performed in collaboration with Québec Transplant, the patients' attending physicians, regional and provincial public health authorities, and the LSPQ reference laboratory. All culture or NAAT-positive samples received, inoculated and processed upon positive culture signal in our laboratory within a three-day timeframe were identified as potential index- or co-contaminated samples. Additionally, patients with positive cultures that were reprocessed with the suspected false positive sample during positive culture media manipulation, and patients with positive cultures that were processed for referral to LSPQ on overlapping periods with the suspected false positive sample, were also identified as potential index- or co-contaminated samples. This approach highlighted specific pre- (prior to sample reception in the laboratory) and per- (during sample processing in the lab) analytical potential cross-contamination events, including those previously described in the literature when various samples are manipulated at the same time (i.e., culture inoculation, positive mycobacteria growth indicator tube [MGIT] media manipulation, aliquoting and shipping) (5,12). This allowed us to identify four additional patients as potential index- or co-contaminated samples. Clinical characteristics, epidemiological risk factors and sample trajectories of these five individuals (n=1 organ donor, n=4 contemporary positive samples) were reviewed from clinical and public health charts and laboratory information systems. Twenty-four loci MIRU-VNTR typing was performed by the PHAC National Microbiology Laboratory (NML) and ONT-based WGS was performed in CHUM for each of these samples (11,13,14).

Investigation outcomes

The ability and relative resolution of both molecular typing systems to further support, or refute, laboratory cross-contamination were assessed. Laboratory procedures at higher risk of cross-contamination were also identified. Cross-contamination was initially suspected when patients without clinical symptoms and epidemiological profiles compatible with

TB had positive samples (patients 1, 2 and 3). Despite testing positive by culture, these patients' primary samples were all negative on smear microscopy and, when available, their follow-up samples were all culture negative, reducing the likelihood of true positive culture results. On the contrary, the results obtained for patients 4 and 5 were considered as potential true positives since these patients had previously lived or transited in TB endemic settings and presented with TB-compatible clinical symptoms. Moreover, patient 5's primary samples were also smear positive (n=3) and NAAT positive (n=2, one sample not tested), and all of their follow-up cultures were also positive, increasing the likelihood of a true positive result. Clinical characteristics and sample trajectories of all patients are reported in **Table 1**. Whole-genome sequence phylogenetic analysis and MIRU-VNTR typing results are presented in **Figure 1**.

Figure 1: Whole-genome sequencing and MIRU-VNTR typing of putative cross-contamination isolates[a,b]



Abbreviations: *M.*, *Mycobacterium*; MIRU-VNTR, mycobacterial interspersed repetitive unit variable number of tandem repeats; WGS, whole-genome sequencing

[a] MIRU-type and whole genome sequencing-derived phylogenetic tree and single nucleotide polymorphism-based distance matrix for all putative contamination isolates. Clustered isolates are highlighted in orange for both typing system results

[b] H37Rv is the *M. tuberculosis* Lineage 4 reference strain

Isolates from patients 1, 2, 3 and 5 had identical MIRU-type and WGS confirmed those isolates to be genetically identical (0 single nucleotide polymorphism [SNP] difference). The isolate from patient 4 had a different MIRU-type and WGS confirmed a significant genetic distance from the other isolates. We retrospectively identified only one bacterial isolate from our laboratory that shared the same MIRU-type as the cluster (patient 6). This patient's isolate was cultured in 2013 from a costal bone sample. Despite sharing a MIRU-type, WGS showed this isolate to have a 13- to 16-SNP distance with the other clustered isolates. Sequencing quality metrics are available in the supplementary materials. Interestingly, this patient had immigrated from the same TB endemic country as patient 5. Confronting epidemiological, clinical and genomic data allowed confirmation that cross-contamination had occurred. Given the convincing epidemiological context, clinical manifestations, stronger smear positivity and positive follow-up cultures, samples from patient 5 were considered to be true positive samples and to represent the index sample or the source of contamination. With identical genotyping but absence of, or incompatible symptomatology and subsequent negative TB test results, patients 1, 2 and 3 were considered to have false positive culture due to cross-contamination. Patient 4, however, was considered TB positive, given the distinct MIRU-type and WGS results.

Patient 2 was never started on TB treatment, given the rapid clinical improvement with anti-staphylococcal therapy. Patient 3 was initially started on TB treatment, which was discontinued after four weeks, as soon as the hypothesis of

Table 1: Patients' clinical presentation and laboratory testing results for *Mycobacterium tuberculosis* pseudo-outbreak

Patient	Clinical presentation	Sample	Sample laboratory trajectory (day)					Complementary laboratory results		
			Sampling	Culture media inoculation	Positive growth	Positive culture media	Reference laboratory send out	PCR	AFB staining	Follow-up cultures and PCR
1	Organ donor	Pre-transplant mycobacterial culture	0	1[a]	20	21[a]	24[a]	Not done	Negative	Negative
2	Intravenous drug user with skin abscess	Superficial wound culture	−1	1[a]	43	32	52	Not done	Negative	Negative
3	Chronic pneumonia	Bronchial aspiration	−3	1[a]	17	18	24[a]	Positive	Negative	Negative
4	Hypermetabolic lung nodules on PET CT	Bronchoalveolar lavage	−12	−12	16	21[a]	24[a]	Negative	Negative	Negative
5	Apical lung consolidation and cavitation	Induced expectorations (a, b, c)	−3	0[a]	6 (a, b) & 7 (c)	8 (a, b) & 9 (c)	10	Positive (b, c)	Positive (a, b, c)	Positive
6	N/A	Costal bone sample	2013	2013	2013	2013	2013	Negative	Negative	N/A

Abbreviations: AFB, acid fast bacilli; N/A, not applicable; PCR, polymerase chain reaction; PET CT, positron emission tomography computerized tomodensitometry

[a] Possible cross-contamination events due to overlapping laboratory procedures. Samples from patients 1, 2, 3 and 5 were received, processed and inoculated on culture media in the same period. Positive mycobacteria growth indicator tube (MGIT) culture media from patients 1 and 4 were opened, aliquoted and smeared on the same day. Samples from patients 1, 3 and 4 were aliquoted and referred to the reference *Laboratoire de santé publique du Québec* (LSPQ) on the same day. Patient 6 was included in the investigation at a later stage since his bacterial isolate was sharing the same mycobacterial interspersed repetitive unit (MIRU)-type as the cluster and this patient's sample had previously been processed in our laboratory

laboratory contamination was raised. As stated above, three patients had received organs from patient 1 (lungs, heart and kidney). They were all initially presumed as having active TB when the donor's sample became culture positive. Given the high risk of unfavourable outcomes in the context of immunosuppression, they were then started on therapy for active TB and had serial follow-ups with infectious disease clinicians. None of them developed TB symptoms. Three months later, when complemented by molecular typing, the results of this investigation were deemed sufficiently convincing by the clinicians to discontinue TB therapy among these organ transplant recipients.

Discussion

As previously reported, cross-contamination of *M. tuberculosis* cultures is not an uncommon event (5,6). A comprehensive and modern approach to investigate *M. tuberculosis* laboratory cross-contamination is presented, including molecular typing, which proved to be the cornerstone in confirming sample contamination directionality. Within the cluster of positive samples examined, WGS showed higher typing resolution than MIRU-VNTR, as was previously reported (15,16). Our investigation led to discontinuation of potentially toxic TB treatments for multiple patients, including immunocompromised transplant recipients for which the implications of a positive TB diagnosis are even more significant (16,17).

Mycobacterium tuberculosis culture cross-contamination may result from its intrinsic ability to create aerosols that survive for extended periods in air and harsh environments, as well as some specific laboratory techniques. In an article published in 2019, the three leading causes of cross-contamination in *M. tuberculosis* culture were human technical errors by laboratory technicians, contamination of reagents and aerosol production (5). An important step in the culture process is decontamination. During this step, bactericidal buffer agents are added to the clinical sample to kill bacterial and fungal flora (18). This technique is specifically prone to cross-contamination. It is usually carried out on specimen batches, as it implies multiple timed steps. Contamination of one of the reagents, often the neutralizing buffer, leads to the inoculation of *M. tuberculosis* in the subsequently processed samples (19). In our laboratory, 14 samples can be decontaminated at a time and we established that contamination of the buffer vial was the most probable vector. This vial could be used over multiple days, leading to possible contamination between samples being decontaminated on separate days, as suspected in our current investigation report. The two other steps where contamination could have occurred are at the opening of positive MGIT media for acid-fast smear growth confirmation and aliquoting prior to sending the sample out to the reference laboratory. Aerosols may be generated during these procedures, since bottles are being reopened near one another. Different methods can be used to reduce the risk of contamination, such as reducing the number of processed samples per batch, disinfecting the common buffer vial between each sample, employing single-use materials and dispensed reagents, using centrifuge caps to limit aerosol production, regular staff training and integrating a negative control in each batch of samples tested (12).

Other reports of *M. tuberculosis* cross-contamination and their investigation are available in literature (6–8,10). The systematic review published in 2019 identified 31 articles describing *M. tuberculosis* cross-contamination events and described the different genotyping methods used. Most of these studies used conventional molecular typing methods, such as IS6110-RFLP, MIRU-VNTR, spoligotyping and direct repeat (DR)-RFLP typing. However, no article in the literature had previously used the nanopore NGS platform for this specific application. In our sample cluster, the latter showed higher typing resolution as one patient with TB reported in 2013 had the same MIRU-type, but clustered with less than 20 SNPs. This patient had immigrated from the same sub-Saharan African country as the pseudo-outbreak index patient, but no epidemiological link could be established between both patients.

Limitations

As in many laboratory contamination events, the success of our investigation relied on initial clinical suspicion that false positive results had been reported. Our investigation then relied on modern genotyping methods, which are becoming more widely available, but still aren't easily accessible everywhere. This is even more of a concern in low-income countries, where *M. tuberculosis* is more prevalent and where sequencing technologies are underutilized (20). Our laboratory serves a population where *M. tuberculosis* incidence is low. In high burden settings, mixed infection and higher active transmission could make it more difficult to clinically identify potential contamination events (21,22).

Conclusion

This investigation highlights the ongoing risk of *M. tuberculosis* cross-contamination in mycobacteria laboratories, including in high-income settings. Combining epidemiological, clinical and molecular data can help resolve contamination events and optimize patient care. *Mycobacterium tuberculosis* WGS shows higher typing resolution than MIRU-VNTR, but typing results from both methods can improve our understanding of contamination directionality between clustered positive samples. Different approaches and methods should be taken to reduce the risk of contamination.

Authors' statement

NL — Conceptualization, methodology, formal analysis, investigation, visualization, writing–original draft
FP — Formal analysis, writing–review & editing
JH — Formal analysis, writing–review & editing

MH — Software, visualization, writing–review & editing
HS — Methodology, software, formal analysis, writing–review & editing
MAL — Conceptualization, methodology, investigation, writing–review & editing
PMA — Methodology, formal analysis, writing–review & editing
SGL — Conceptualization, methodology, validation, resources, data curation, project administration, funding acquisition, visualization, supervision

Competing interests

None.

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Passing of Dr. Paul Varughese

8 Sept. 1945 – 14 Sept. 2024

Dr. Paul Varughese, a long-time and beloved Public Health Agency of Canada employee, passed away on September 14, 2024.

Trained as a veterinarian in his native India, Dr. Varughese moved to Saskatchewan, Canada to continue his studies, where he became one of Canada's foremost experts on vaccines and vaccine preventable disease (VPD). He led many national VPD files, including congenital rubella syndrome, adolescent pertussis vaccine booster and the investigation of influenza vaccine adverse events, and represented Canada at many Pan American Health Organization and World Health Organization events. He also helped pilot the inaugural years of the Canadian Field Epidemiology Training Program (FETP), now called the Canadian Field Epidemiology Program (CFEP). In addition to his many scientific and research contributions, Dr. Varughese was also a sought-after mentor, providing guidance and wise counsel to junior staff. With his multiple decades of experience at Health Canada and the Public Health Agency of Canada, he was a wealth of important historical public health information. Even after his retirement in 2011, he continued to contribute as a senior science advisor.

He is remembered fondly as a colleague who was always approachable, interested in others and generous with his time.

Epidemiological analysis of paediatric tuberculosis infection in northern Saskatchewan First Nations communities, 2018–2022

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Abstract

Background: Paediatric tuberculosis (TB), or TB in children younger than 15 years of age, is a growing public health concern in First Nations communities.

Objective: To describe the epidemiology of paediatric TB in northern Saskatchewan's on-reserve First Nations communities.

Methods: We examined the paediatric TB cases reported in northern Saskatchewan First Nations on-reserve communities from 2018 to 2022 using the Northern Inter-Tribal Health Authority database. We employed descriptive statistics to understand the paediatric TB epidemiology in these susceptible populations.

Results: Sixty paediatric TB cases were identified over the study period: four cases in 2018, six cases each in 2019 and 2020, 16 cases in 2021 and 28 cases in 2022. The average annual incidence was 112.6 cases per 100,000 children, ranging from 36.1 in 2018 to 268.6 in 2022. Children younger than five years of age constituted 55% of cases, with males comprising 60%. The Far North Central and East zones accounted for 90% of cases. Most cases (85%) were detected through contact tracing and pulmonary TB comprised 85% of cases. Of these, 71% completed therapy, while 27% were still in treatment. Cases were predominantly from communities with low education (100%), inadequate housing (67%) and low income (67%).

Conclusion: Paediatric TB incidence among First Nations in northern Saskatchewan is increasing, especially among children younger than five years of age. Our study identifies disparities in paediatric TB incidence across demographics and geographic areas, suggesting that reducing the disease burden requires a combination of community- and person-driven TB initiatives.

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Keywords: tuberculosis, paediatric tuberculosis, First Nations, northern Saskatchewan

Introduction

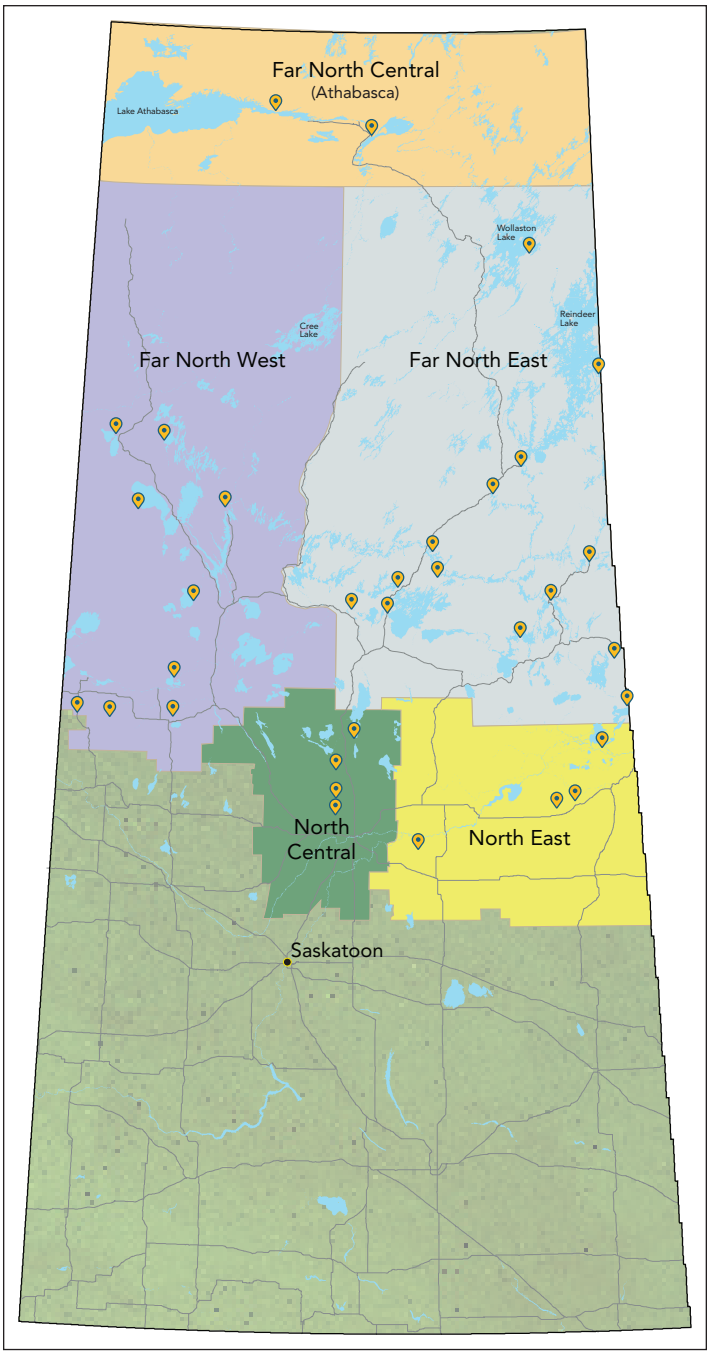
The public health issue of tuberculosis (TB) persists despite being treatable and preventable (1). Tuberculosis in children younger than 15 years of age, also referred to as paediatric TB, has historically received little attention (2–4). Several studies have suggested that the true paediatric TB burden has been incorrectly estimated because a higher proportion of extra-pulmonary TB patients are not reported (2,5). Recent statistics indicate that in 2022, children younger than 15 years of age accounted for 12% of all TB cases reported worldwide (6).

In Canada, 7% of all reported TB cases in 2022 were paediatric (7). This statistic underscores the relatively lower incidence of TB in children within the national context, contrasting with higher proportions observed in specific subpopulations. For example, in Canada, children of Indigenous descent constituted 61% of all paediatric TB cases in 2019. Within this group, First Nations children specifically represented 25% of the total paediatric TB cases (3). In Saskatchewan, First Nations children younger than 15 years of age comprised 21% of all active TB cases in 2020 (8). Paediatric TB has shown an increasing trend within Saskatchewan's First Nations communities (9). By 2022, 45% of active TB cases in these communities were younger than 15 years of age, reflecting a 74% rise compared to 2021 (9).

Moreover, research shows that paediatric TB infections are challenging to recognize early and require immediate care since they have a higher risk of severe outcomes (1,3,4,10). Understanding the epidemiology of paediatric TB and the effects of current TB control methods is crucial for addressing the difficulties. This is particularly critical given the discontinuation of Bacille Calmette-Guérin (BCG) vaccination, a key component of the TB elimination strategy for infants in high TB incidence areas in Canada (11). Notably, routine BCG vaccination was discontinued among on-reserve First Nations infants in high-TB incidence communities in northern Saskatchewan in September 2011 (12).

Few studies (13,14) have examined paediatric TB in Canadian First Nations communities and there are still gaps in our understanding of how clinical and socioeconomic factors affect the current paediatric TB epidemic among northern Saskatchewan First Nations on-reserve. Our literature review identified a gap in research specifically addressing paediatric TB in First Nations communities in northern Saskatchewan, despite reported TB outbreaks in the region (15,16). This underscores the urgent need to assess and understand the paediatric TB situation in this vulnerable population to tailor appropriate interventions suited to local circumstances. Thus, our study aimed to provide an epidemiological description of paediatric TB among on-reserve First Nations communities in northern Saskatchewan.

Figure 1: Map of geographic zones[a] of northern on-reserve Saskatchewan First Nations communities



[a] Five geographic zones: Far North Central depicted in peach, Far North West in purple, Far North East in grey, North East in yellow and North Central in green

Methods

Study population and sites

Our study was carried out in First Nations communities in northern Saskatchewan. In the region, there are 33 First Nation communities situated on reserves, collectively housing approximately 55,000 residents, with close to one-quarter of them younger than 15 years of age (17). **Figure 1** illustrates these communities categorized into five geographic zones: Far North Central, Far North West, Far North East, North East and North Central. The on-reserve First Nations communities within these geographic zones fall under the jurisdiction of the Northern Inter-Tribal Health Authority (NITHA). This organization collaborates closely with Community Bands and Tribal Councils to deliver a comprehensive range of public health services, aiming to enhance the health and well-being of the First Nations population. These services encompass communicable disease control, immunization, specialized program support, research initiatives, ongoing health status monitoring, training programs, disease surveillance and other technical assistance (17).

The study population was restricted to and included all those younger than 15 years of age with a clinical diagnosis of TB or laboratory-confirmed results in the study area (10,18). Clinical diagnosis relied on a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA), abnormal chest x-ray, contact history and clinical symptoms including prolonged fever, persistent cough and failure to thrive (3). The positive results of sputum Acid-Fast Bacilli (AFB) smear microscopy and the culture for confirmation were used to make the laboratory diagnosis (3,15,19).

Data collection

We analysed the epidemiological trend and characteristics for paediatric TB in the study group. De-identified individual-level demographic and clinical data of reported confirmed paediatric TB cases from 2018 and 2022 were extracted from the NITHA TB surveillance database. The database is a comprehensive repository that serves as a crucial resource, systematically documenting epidemiological information and clinical profiles related to TB cases within First Nations communities in northern Saskatchewan. The utilization of this database ensures rigorous data integrity and facilitates in-depth analyses essential for understanding and addressing TB challenges in this specific population. The community-level data used in this study were from the 2016 First Nations Community Well-Being index statistics (20). Based on the 2016 Census of Canada, Indigenous Services Canada created the publicly accessible Community Well-Being estimates used in this study (20).

Study variables

The demographic factors at the individual level that were examined included the client's age, sex and geographic zone (**Table 1**). The clinical parameters that were taken into account in this study were case detection year, TB history, disease site, method of detection, BCG vaccination, clinical outcomes and treatment status. According to the healthcare provider's treatment audit, TB treatment regimens administered under Directly Observed Therapy that were successfully completed were deemed to be treated in our study. In contrast, those still receiving treatment were considered to be on treatment. Those who did not finish their TB therapy but passed away while receiving it were considered to have died during treatment. In our study, we used community-level metrics such as housing score, education score and income score, which varied from zero to 100 (21). The adequacy of housing, based on the percentage of a community's population residing in homes that are not overcrowded and do not require major repairs, is referred to as the housing score (adequate housing level; Table 1). The percentage of a community's population with a high school diploma or higher was used to calculate the education score (community education level; Table 1). The percentage of the community's per capita income was used to compute the income score (community income level; Table 1) (21). Based on each of these community-level factors, communities were classified as low (less than 50 points) or high (50 or more points) (21).

Table 1: Summary of study variables

Variable name	Variable description	Variable classification
Outcome variable		
Active TB	Children younger than 15 years of age diagnosed with active TB	Counts
Individual-level variables		
Age	Child's age at TB diagnosis	Categorical; 0–4 years, 5–9 years, 10–14 years
Sex	Sex of the paediatric active TB client at birth	Categorical; male, female
Geographic zone	Geographic location of participants by zone	Categorical; Far North Central, Far North East, Far North West, North East
Year	Year the TB case was diagnosed	Categorical; 2018, 2019, 2020, 2021, 2022
Prior history of TB	Previous active or latent TB infection	Categorical; yes, no
Disease site	Location of TB infection	Categorical; pulmonary, disseminated, lymphatic/ meningitis
Method of detection	How active TB was identified	Categorical; contact investigation, symptomatic, screening
BCG vaccination	Whether BCG was received	Categorical; yes, no, unknown
Treatment status	Current TB treatment state	Categorical; completed treatment, on treatment, died during treatment
Hospitalization	Ever had TB related hospital admissions	Categorical; yes, no
Community-level variables		
Adequate housing level	Proportion of a community's residents who live in uncrowded, reasonably maintained homes	Categorical; high (50 or more points) or low (less than 50 points)
Community education level	Percentage of a community's residents with a high school diploma or higher	Categorical; high (50 or more points) or low (less than 50 points)
Community income level	Community's income per capita expressed as a percentage	Categorical; high (50 or more points) or low (less than 50 points)

Abbreviations: BCG; Bacille Calmette-Guérin; TB, tuberculosis

Data analysis

Descriptive statistical analyses were carried out utilizing TB data from northern Saskatchewan First Nations communities. The frequency and percentage of paediatric TB cases were computed and tabulated based on both individual and community-level variables. The annual paediatric TB incidence per 100,000 children younger than 15 years old for the research period was calculated. To estimate the TB incidence, we divided the number of new paediatric TB cases that occurred during the specified time period by the total study population at risk (children younger than 15 years of age) multiplied by

100,000 children. Further, age- and sex-based paediatric TB incidence rates per 100,000 children were estimated for each year during the study period. All statistical data analyses were carried out using STATA version 17.0 (StataCorp LLC, Texas, United States). Line graphs displaying paediatric TB incidence were created with Microsoft Excel version 2021(Microsoft Corporation, Washington, United States).

Results

Overall, we identified 60 paediatric TB cases among children younger than 15 years of age between 2018 and 2022 in northern Saskatchewan First Nations on-reserve communities. The data showed a significant upward trend in the reported cases: there were four cases (7%) in 2018, increasing to six cases (10%) in both 2019 and 2020, 16 cases (27%) in 2021 and 28 cases (47%) in 2022. **Table 2** further showed that among paediatric TB cases, children younger than the age of five made up the majority (55%) of the cases, followed by those between the ages of five and nine years (35%) and 10 and 14 years (10%). According to Table 2, 60% of paediatric TB cases were male and 40% were female. Another aspect of this study was geographical variation. Forty-seven percent of paediatric TB cases lived in the Far North East zone, while 43% were in the Far North Central zone. The remaining paediatric TB clients were located in the Far North West (8%) and North East (2%) zones.

Over a five-year period, the average paediatric TB incidence was 112.6 cases per 100,000 children each year. The paediatric TB incidence in children aged 0–4 years (277.6 cases per 100,000 children) was also greater than that in children aged 5–9 years (103.7 cases per 100,000 children) and in children aged 10–14 years (28.4 cases per 100,000 children). Males (132.7 cases per 100,000 children) had a higher average annual paediatric TB incidence during the study period compared to females (91.8 cases per 100,000 children). The Far North Central region had the greatest average annual incidence of paediatric TB (696.1 cases per 100,000 children), followed by the Far North East (116.8 cases per 100,000 children), the Far North East (47.0 cases per 100,000 children) and the North East (11.4 cases per 100,000 children) (**Table 3**).

The active paediatric TB incidence increased by 644.0% from 36.1 cases per 100,000 children in 2018 to 268.6 cases per 100,000 children in 2022 (**Figure 2**). Between 2018 and 2022, the paediatric TB incidence in the 0–4 year age group (from 70.8 cases per 100,000 children to 912.8 cases per 100,000 children) and the 5–9 year age group (from 23.9 cases per 100,000 children to 178.9 cases per 100,000 children) increased by 1,189.3% and 648.5%, respectively. The paediatric TB incidence in children aged 10–14 years declined by 6%, from 24.7 cases per 100,000 children in 2018 to 23.1 cases per 100,000 children in 2022 (Figure 2).

Table 2: Distribution of active paediatric tuberculosis cases by demographic characteristics in northern Saskatchewan First Nations communities, 2018–2022

Demographic characteristics	Active paediatric TB cases	
	Total number of cases (n=60)	Percentage
Year		
2018	4	7%
2019	6	10%
2020	6	10%
2021	16	27%
2022	28	47%
Age group (years)		
0–4	33	55%
5–9	21	35%
10–14	6	10%
Sex		
Male	36	60%
Female	24	40%
Geographic zone		
Far North Central	26	43%
Far North East	28	47%
Far North West	5	8%
North Central	0	0%
North East	1	2%

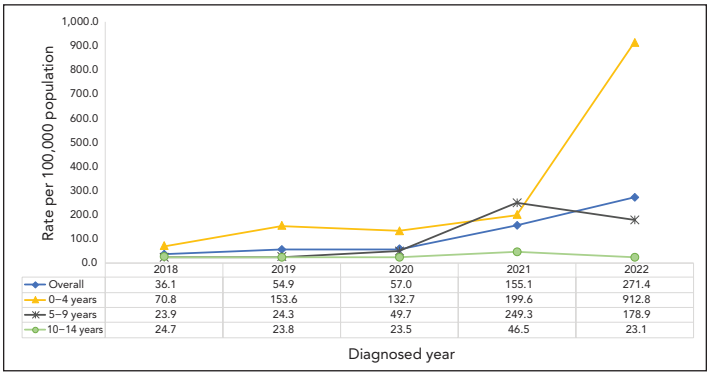
Abbreviation: TB, tuberculosis

Table 3: Distribution of active paediatric tuberculosis and incidence by demographic characteristics in northern Saskatchewan First Nations communities, 2018–2022

Demographic characteristics	Average annual paediatric TB cases (n)	Population of children under 15 years (N)	Average paediatric TB incidence per year (per 100,000 children)
Total	12	10,653	112.6
Age group (years)			
0–4	6.6	2,377	277.6
5–9	4.2	4,051	103.7
10–14	1.2	4,226	28.4
Sex			
Male	7.2	5,227	132.7
Female	4.8	5,426	91.8
Geographic zone			
Far North Central	5.2	747	696.1
Far North East	5.6	4,794	116.8
Far North West	1.0	2,130	47.0
North Central	0.0	1,229	0.0
North East	0.2	1,753	11.4

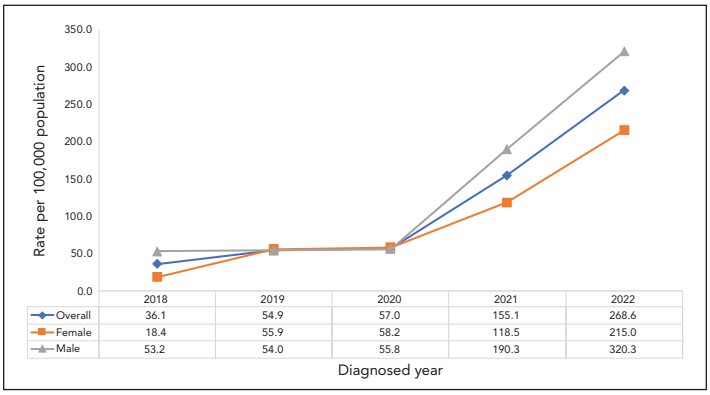
Abbreviation: TB, tuberculosis

Figure 2: Active paediatric tuberculosis incidence by age group in northern Saskatchewan First Nations on-reserve communities, 2018–2022



Although the paediatric TB rates in both sexes showed an upward trend over the study period between 2018 and 2022 in the northern Saskatchewan First Nations communities, the percentage annual change was higher among females (**Figure 3**). The paediatric TB rate in females increased by 1,068%, from 18.4 cases per 100,000 children in 2018 to 215.0 cases per 100,000 children in 2022, whereas male paediatric TB rate increased by 502%, from 53.2 cases per 100,000 children in 2018 to 320.3 cases per 100,000 children in 2022.

Figure 3: Active paediatric tuberculosis incidence by sex in Northern Saskatchewan First Nations on-reserve communities, 2018–2022



The majority of paediatric TB cases, 58 of 60 cases (97%), had no history of prior TB infection (**Table 4**). The majority (85%) of paediatric TB clients were pulmonary TB. Disseminated TB (8%) and lymphatic or meningitis TB (7%) accounted for a relatively small number of paediatric TB cases. Additionally, 85% of paediatric TB cases were detected through contact investigations as opposed to 13% and 2% of paediatric TB cases identified by symptomatic and screening investigations, respectively (Table 4). Given that BCG has not been used since 2011 among northern Saskatchewan First Nations communities on reserves, only 3% of participants self-reported having received a BCG vaccination, compared to 90% of those who had no BCG documentation.

Table 4: Distribution of paediatric tuberculosis cases by clinical characteristics in Northern Saskatchewan First Nations on-reserve communities, 2018–2022

Clinical characteristics	Active paediatric TB cases	
	Number of cases (n=60)	Percentage
Prior history of TB		
Yes	2	3%
No	58	97%
Disease site		
Pulmonary	51	85%
Disseminated	5	8%
Lymphatic/meningitis	4	7%
Method of detection		
Contact investigation	51	85%
Symptomatic	8	13%
Screening	1	2%
BCG vaccination		
No	4	7%
Yes	2	3%
Unknown	54	90%
Treatment status		
Completed	43	71%
On treatment	16	27%
Died during treatment	1	2%
Hospitalizations		
Ever hospitalized	15	25%
No admissions	45	75%

Abbreviations: BCG, Bacille Calmette-Guérin; TB, tuberculosis

At the end of the study period, 27% of paediatric TB cases were still receiving treatment, 71% had successfully finished Directly Observed Therapy and 2% had died while receiving treatment. Only one-quarter (25%) of paediatric TB cases have ever been admitted to the hospital for tuberculosis-related reasons (Table 4).

Table 5 presents the distribution of active paediatric TB cases across various community characteristics. The analysis reveals significant disparities across various socioeconomic factors. Communities with a high level of adequate housing reported 20 cases (33%), whereas those with a low level had 40 cases (67%). Similarly, the income level analysis showed that communities with high income levels had 20 cases (33%), while those with low-income levels had 40 cases (67%). Regarding education, all cases (100%) occurred in communities with low education levels.

Table 5: Distribution of active paediatric tuberculosis cases by community-level characteristics in Northern Saskatchewan First Nations communities, 2018–2022

Community characteristics	Active paediatric TB cases	
	Number of cases (n=60)	Percentage
Adequate housing level		
High	20	33%
Low	40	67%
Community education level		
High	0	0%
Low	60	100%
Community income level		
High	20	33%
Low	40	67%

Abbreviation: TB, tuberculosis

Discussion

This study was carried out in First Nations on-reserve communities in northern Saskatchewan to shed light on the factors that influence the paediatric TB distribution over time. To deliver context-specific TB care, our analysis identified the characteristics of paediatric TB cases among First Nations children in these communities.

The estimated paediatric TB rate in this study (112.6 cases per 100,000 children) was higher than the paediatric TB rates among all Canadian First Nations children residing on reserves (20.2 cases per 100,000 children) and that of the general population of children in Canada (1.2 cases per 100,000 children) (18). The disproportionately higher rate among this study group could be linked to malnutrition, possibly exacerbated by persistent food insecurity prevalent in First Nations communities. This condition increases the susceptibility of children to developing TB following exposure (14,22). Prior studies indicate that the increased incidence of paediatric TB could stem from ongoing shortages and frequent turnover among healthcare staff specializing in TB (14,15,23). These workforce challenges can result in delays in both diagnosing the disease and initiating treatment (14,15,23).

A Canadian study (18) reported that 50.5% of paediatric TB cases were male; however, this study found a higher proportion of paediatric TB cases among males (60%). Our study revealed patterns of increased paediatric TB incidence in both sexes, with particularly higher rates among males. Several factors may contribute to this disparity. Previous research has suggested that physiological differences and behavioral patterns between males and females could affect TB susceptibility and progression in males (24,25). However, a study reported no significant difference in TB incidence between male and female children under 15 years of age (26). Given the varied findings, assessing the overall contribution of sex-specific differences in tuberculosis incidence remains challenging. Future research should prioritize sex-specific investigations into paediatric TB incidence to better understand the underlying factors contributing to the observed disparities.

The majority of paediatric TB cases in this study were among children younger than five years, which is consistent with an earlier study (14). The escalating trend of paediatric TB cases among children younger than five years compared to older age cohorts in the study group warrants careful examination. Younger children have shown higher susceptibility to TB due to several factors. Firstly, children younger than five years have developing immune systems, making them more vulnerable to infections including TB (14,27–29). Secondly, household transmission dynamics can lead to increased exposure among younger children who are in close contact with infectious adults (3). Thirdly, diagnostic challenges such as difficulties in obtaining adequate sputum samples for testing contribute to delayed or missed diagnoses in this age group (3,4). The delayed or missed diagnosis can lead to progression of TB infection into life-threatening forms, including disseminated TB and TB meningitis (14,29). Beyond diagnostic challenges with obtaining samples as outlined below, it should be noted that children this young are often asymptomatic or present with vague symptoms and often, their cultures, even if obtained, are of lower yield, as they tend to be paucibacillary. Also, children in this age group are just generally at higher risk for higher morbidity and mortality with TB disease progression.

The total number of paediatric TB cases in Saskatchewan's northern First Nations population living on reserves over the study period were reported in four different geographic areas. Most of the paediatric TB cases in this study were reported in the Far North Central and Far North Eastern regions; perhaps the communicability of TB and location may have influenced the TB incidence of as suggested in other studies (18,30). The Northern Saskatchewan First Nations TB Program relies on the expertise of TB nurses, community health nurses, lay TB workers and a medical health officer to provide timely, safe and competent TB care. However, the program's effectiveness maybe hindered by inadequate staffing and challenges in accessing healthcare in remote First Nations settings (17). Similar studies indicate a connection between geographical discrepancy and a shortage of TB healthcare experts, difficulties with patient transportation and logistics (15,30). The disparity in paediatric TB incidence between geographic areas may also be explained by community social networks that increase susceptibility to TB infection and challenging obstacles to seeking and pursuing TB care (28). Furthermore, the remoteness of communities may exacerbate issues including access to healthcare and early TB diagnosis and treatment, as suggested in previous studies (14,30).

Most paediatric TB cases in our study were pulmonary TB, which is consistent with other studies (18). This is possibly because of the immune system weakness that has been linked to TB predisposition in children, as described in prior studies (31,32). Similar to our analysis, a substantial number of the paediatric TB cases required hospitalization (18,33). These hospitalizations are likely due to the challenges in identifying TB symptoms in young children, who often present with nonspecific clinical signs. Such challenges can lead to diagnostic delays and potentially exacerbate disease outcomes (3).

Similar to prior studies conducted in Canada, our study demonstrates that contact investigations uncovered the majority of paediatric TB cases living in northern Saskatchewan First Nations on-reserve communities (15,18). In order to further improve contact investigation, it is necessary to overcome challenges such perceived TB stigma, understaffed TB workers and contacts' poor TB knowledge (28,32–37).

Additionally, our study provided evidence to support the fact that living conditions are subpar on reserves. According to previous research, inadequate housing, low rates of higher education and low-income level all contribute to the persistence of TB transmission (30,38). In our study, paediatric TB cases were stratified by community-level characteristics and disparities were examined similar to a prior study (38). The level of overcrowded and inadequate housing in the community may have affected the frequency of paediatric TB clients. Our study found that people from First Nations on-reserve communities with lower adequate housing had the highest occurrence of paediatric TB cases. Our findings are consistent with past studies that emphasized the important role that homelessness and crowded and/or poorly maintained dwellings play in the transmission of TB (15,29,30,39). Given the high rates of substandard housing and overcrowding, which were identified in First Nations on-reserve communities in a prior study, this was expected (30,40). A comparable study has observed the impact of family structure and culture on large households (41–43), and this may play a role given that First Nations People on-reserve often have large families and therefore more children living in relatively small dwellings (44).

The findings of our study are consistent with other research in that people who live in communities with higher levels of education are probably less likely to experience paediatric TB incidences (45). The trauma experienced in residential schools may account for the low community education levels, as documented in a previous study (14). Communities with higher percentages of individuals possessing advanced education may exhibit greater knowledge about the causes, risk factors, symptoms and treatments of TB. This enhanced awareness can influence one's frequency of seeking medical assistance and adherence to TB prevention measures (45).

Finally, the results of our study supported prior research (30) that suggested a connection between community income level and the incidence of TB, showing that paediatric TB cases were more common among residents of lower-income communities. This study's findings are consistent with notions that TB is a social sickness, with major medical repercussions, that is fueled by poverty (14). A lower degree of community income can lead to more TB cases by resulting in food insecurity and impeding access to health care through transportation cost, as well as other related economic costs (14).

Study strengths and limitations

This study used high-quality data to address the local TB context and epidemiology in First Nations communities. We evaluated the trend of paediatric TB over a five-year period for the first time among First Nations communities in northern on-reserve Saskatchewan communities. It becomes increasingly challenging to identify, stop and eventually eradicate TB among individuals who are most at risk. Perhaps these challenges are a result of the dearth of current, reliable and trustworthy information regarding the background risk of paediatric TB among First Nations peoples at the community level (23).

Due to a lack of available data, we excluded certain variables from our study. For instance, prior research has linked cultural factors, historical colonial trauma and food instability to the persistence of TB transmission (14,30,44) but these factors were not taken into account in our study due to lack of data. More research is required to promote culturally acceptable TB care practices that respect cultural diversity and foster an inclusive atmosphere in First Nations communities. Future studies should employ rigorous analytical methods to mitigate the limitations in establishing causal relationships or pathways observed in this study. The generalizability of our findings may be constrained by the specific context of the study population. Additionally, the dichotomous nature of the Community Well-being Index data used in our study might restrict nuanced interpretations of community conditions.

Public health implications

The evidence from this study suggests that First Nations communities in northern Saskatchewan are experiencing an increase in paediatric TB cases. To improve paediatric TB control and care in northern Saskatchewan First Nations communities, public health professionals will potentially benefit from the findings of our study in terms of its implication on risk factors and contact tracing investigations. According to past studies, the insight from this study can aid in the rapid identification of paediatric TB, which may lower the severity of the patient's illness and possibly halt widespread paediatric TB infections among households and within the community (46).

Despite these steps, an earlier study viewed them as short-term solutions for stopping TB transmission within the northern Saskatchewan First Nations population (47). If eradication is the long-term objective, then dealing with the socioeconomic problems identified in this study, poverty, inadequate housing

and education, that have contributed to the spread of TB is imperative (14). As indicated in an earlier study, more housing must be built and current housing must be repaired in order to address these concerns (48). Additionally, as revealed in a prior study, boosting food and other incentive programs may help combat the spread of TB in low-income communities (48,49). Promoting higher education and increasing TB awareness, as proposed by a previous study, will help to minimize stigma and discrimination (14,50,51). These efforts may increase the uptake of TB care and preventive services in northern Saskatchewan First Nations communities.

Conclusion

Paediatric TB continues to disproportionately impact First Nations communities in northern Saskatchewan, a gap that may be mostly attributable to social determinants of health. Four of the five geographical zones in this study exhibited a significant burden of paediatric TB cases. This study found that paediatric TB rates were higher in males than in females and highest in children younger than five years. This study emphasizes the critical need to successfully address the long-standing socioeconomic problems in the community, like poverty, inadequate housing and inadequate education, which significantly contribute to the spread of TB. It also highlights the importance of contact investigation in the early detection of new paediatric TB infections. This research demonstrates that combining community-based and individual-focused TB initiatives can lead to substantial progress.

Authors' statement

NN — Conceptualization, investigation, visualization, writing–review & editing, supervision
ED — Conceptualization, data extraction and analysis, writing–original draft, writing–review & editing
RT — Conceptualization, writing–review & editing
GA — Conceptualization, writing–review & editing, supervision
TC — Investigation, writing–review & editing
TA — Investigation, writing–review & editing
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Competing interests

None.

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