Epidemiology, clinical features and outcomes of incident tuberculosis in children in Canada in 2013–2016: results of a national surveillance study

Shaun K Morris ^{1,2,3} Ryan J P Giroux,^{2,3} Raquel Consunji-Araneta,⁴ Kristoffor Stewart,⁵ Maureen Baikie,⁶ Fatima Kakkar,⁷ David Zielinski,⁸ Alena Tse-Chang,^{9,10} Victoria J Cook,^{11,12} Dina A Fisher,¹³ Marina I Salvadori,^{14,15} Jeffrey M Pernica ¹⁶ Laura J Sauve,^{12,17} Charles Hui,¹⁸ Amber Miners,¹⁹ Gonzalo G Alvarez,^{20,21} Assaad Al-Azem,^{22,23} Victor Gallant,²⁴ Barbara Grueger,¹³ Ray Lam,^{1,2} Joanne M Langley,^{25,26} Nicole Radziminski,²⁷ Elizabeth Rea,²⁸ Sam Wong,^{9,27} Ian Kitai^{1,2}

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For numbered affiliations see end of article.

Correspondence to

Dr Shaun K Morris, Infectious Diseases, The Hospital for Sick Children, Toronto, Canada; shaun.morris@sickkids.ca

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ABSTRACT

Purpose Childhood tuberculosis disease is difficult to diagnose and manage and is an under-recognised cause of morbidity and mortality. Reported data from Canada do not focus on childhood tuberculosis or capture key epidemiologic, clinical and microbiologic details. The purpose of this study was to assess demographics, presentation and clinical features of childhood tuberculosis in Canada.

Methods We conducted prospective surveillance from 2013 to 2016 of over 2700 paediatricians plus vertical tuberculosis programmes for incident tuberculosis disease in children younger than 15 years in Canada using the Canadian Paediatric Surveillance Program (CPSP).

Results In total, 200 cases are included in this study. Tuberculosis was intrathoracic in 183 patients of whom 86% had exclusively intrathoracic involvement. Central nervous system tuberculosis occurred in 16 cases (8%). Fifty-one per cent of cases were hospitalised and 11 (5.5%) admitted to an intensive care unit. Adverse drug reactions were reported in 9% of cases. The source case, most often a first-degree relative, was known in 73% of cases. Fifty-eight per cent of reported cases were Canadian-born Indigenous children. Estimated study rates of reported cases (per 100 000 children per year) were 1.2 overall, 8.6 for all Indigenous children and 54.3 for Inuit children.

Conclusion Childhood tuberculosis may cause significant morbidity and resource utilisation. Key geographies and groups have very high incidence rates. Elimination of childhood tuberculosis in Canada will require well-resourced community-based efforts that focus on these highest risk groups.

BACKGROUND

Globally, there were an estimated 10 million new cases and 1.4 million tuberculosis (TB)-related deaths in 2018.¹ In Canada, there are on average 1800 incident cases of TB disease per year with approximately 3% of disease occurring in children younger than 15 years.² In Canada, Indigenous peoples and foreign-born individuals are

What is already known on this topic?

- ⇒ Childhood tuberculosis is under-reported and under-researched but, globally, is a major hidden cause of childhood mortality.
- ⇒ According to the Public Health Agency of Canada, childhood tuberculosis accounts for about 3% of all cases in the country.
- ⇒ National data lacked important clinical, treatment and epidemiological detail including methods of diagnosis that is needed to improve diagnosis, management and control.

What this study adds?

- ⇒ This study prospectively surveyed clinicians and programs managing childhood tuberculosis and provides more epidemiologic and clinical detail than published Canadian data.
- ⇒ There is substantial variation in regional incidence and remarkably high rates of tuberculosis in Indigenous Canadians who accounted for more than half of cases.
- ⇒ This study demonstrated high rates of hospitalisation, central nervous system infection with intensive care unit admission and a substantial rate of adverse drug reactions.

disproportionately affected by TB.³ Compared with adult TB, childhood TB disease is more difficult to diagnose, presents unique management challenges^{4,5} and is an under-recognised cause of morbidity.^{6,7}

TB is a reportable disease at the federal and provincial/territorial levels in Canada. However, available data do not capture important details including the type of disease, use and results of diagnostic tests, rates of culture confirmation and hospitalisation, follow-up data, rates of adverse drug reactions (ADRs), rates in specific childhood populations and whether source cases were identified. To address these gaps, we conducted a multi-year prospective surveillance study of incident TB

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disease in children under the age of 15 in Canada using the Canadian Paediatric Surveillance Program (CPSP). Additional pertinent background information is given in the online supplemental appendix.

METHODS

The CPSP, a joint project of the Public Health Agency of Canada (PHAC) and the Canadian Paediatric Society, conducts active monthly national surveillance of over 2700 participant paediatricians and paediatric subspecialists for certain childhood disorders. For this study, we also included non-paediatricians from the TB programmes of Alberta, Saskatchewan, Nunavut, the Northwest Territories and British Columbia. We aimed to identify incident cases of childhood TB between October 2013 and September 2016 and follow-up every 6 months until 6 months post-treatment completion. Pertinent data from the TB programme at Hôpital Sainte-Justine in Montréal, Québec, were retrospectively obtained in May 2017 outside of the CPSP platform. The protocol (<https://www.wcpspcpsca/uploads/studies/childhood-TB-protocol.pdf>) initially used existing international case definitions for the diagnosis of intrathoracic childhood TB,⁸ however, revised criteria for intrathoracic TB were published in 2015 so we reviewed and reclassified all cases as confirmed or unconfirmed by consensus adjudication by three authors (SKM, RJPG, IK) according to the new criteria.⁹

We calculated population-based age-specific rates of reported cases using 2016 population data¹⁰; for those <1 year of age we used number of live births. Due to potential under-reporting, rates presented here represent the lowest possible estimate of incidence of childhood TB for specific groups. Rates for Indigenous populations were calculated using denominators from Statistics Canada Aboriginal Population Profile.¹¹ Details of study's ethics approvals are provided in the online supplemental appendix.

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FINDINGS

From October 2013 to September 2016, an average of 2536 monthly reporting forms were sent by CPSP and response rates averaged 81%. The number reported and reasons for exclusions are shown in figure 1 and 200 cases met the study case definition. Eighty cases (40%) were microbiologically confirmed and 116 (58%) were categorised as unconfirmed. The remaining 4 cases were categorised as presumed or difficult to classify. Sixty-six (36%) and 20 (53%) of intrathoracic and extrathoracic cases, respectively, were microbiologically confirmed.

The calculated minimum overall rate of reported cases of childhood TB during the study period was 1.2 per 100 000 per year compared with an approximate notification rate to PHAC of 1.6/100 000.¹¹ Comparisons with data reported by the PHAC are shown in the online supplemental appendix. Key demographics of cases reported to CPSP are shown in table 1. Reports by age group were 2.4 per 100 000 live births in children under 1 and 1.8, 0.6 and 0.9 per 100 000 population for the age groups 1–4, 5–9 and 10–14 years, respectively. Most cases (n=116, 58%) occurred in Canadian-born Indigenous children, the majority of whom were identified as First Nations (67%) or Inuit (30%). The reported case rate in all Indigenous children was 8.6/100 000/year with the highest rate being in Inuit children (54.3/100 000/year) (table 2).

*Deleted refers to case notifications that were deleted by the CPSP primarily for clerical reasons

^Discarded refers to case notifications that the reporting physician or healthcare professional was unable to complete the questionnaire, often because they no longer followed the patient or could not recall the case

#Excluded refers to case notifications that were noted to not meet inclusion criteria. When excluded by the CPSP, this was primarily due to age 15+ years. When excluded by the Study Investigators, there were multiple demographic and clinical exclusions.

°No Response refers to case notifications that were sent questionnaires and reminders but did not return a questionnaire or correspond further with the CPSP

⊃Duplicates were noted either by the CPSP program or by comparison of case demographics (sex, birth date, province/territory of residence)

Figure 1 Flowchart of cases notified, excluded and included. CPSP, Canadian Paediatric Surveillance Program.

Forty-three (22%) of reported cases were in Canadian-born non-Indigenous children. Thirty children (15%) were born outside of Canada of whom 13 (43%) were born in sub-Saharan Africa. Among the foreign-born, Africa was the most common continent, and the Philippines and India were the most common countries of birth (table 1). The rates of reported cases for foreign-born and Canadian-born children with at least one foreign-born parent were 2.7 and 1.4 per 100 000, respectively. Of Canadian-born non-Indigenous children, 14 (26%) travelled to an endemic country.

Most cases resided in Manitoba (n=62, 31%) followed by Ontario (n=32, 16%), Québec (n=28, 14%) and Nunavut

Table 1 Demographic features of cases

	Number (n)	%
Age (N=200)		
<1	28	14
1 to 4	82	41
5 to 9	36	18
10+	54	27
Sex (N=196)		
Male	99	50.5
Female	97	49.5
Ethnicity (N=200)		
Canadian born, Non-Indigenous	43	21.50
Canadian born, Indigenous, total	116	58
Canadian born, First Nations	(78)	(39)
Canadian born, Inuit	(35)	(17.5)
Canadian born, other	<5	n/a
Canadian born, Not Specified	11	5.5
Non-Canadian born, total (country or region of birth)	30	15
Africa	(13)	(6.5)
Philippines	(10)	(5)
South Asia	(5)	(2.5)
Other	<5	n/a

Table 2 Rates of reported case rates by province or territory of residence and Indigenous status

	Rate per 100 000	0–14 Population size	Cases (n)
Canada (N=200)			
Canada (N=200)	1.2	5 778 929	200
Province/territory of residence			
British Columbia	0.4	691 495	8
Alberta	0.9	764 638	21
Saskatchewan	3.1	213 796	20
Manitoba	8.5	243 534	62
Ontario	0.5	2 221 986	32
Québec	0.7	1 273 093	28
Atlantic Provinces*	n/a	343 482	<5
Nunavut	80.6	11 582	28
Indigenous status†			
Indigenous overall	8.6	448 865	116
First Nations overall	9.1	285 825	78
First Nations on-reserve	20.2	105 445	64
Inuit	54.3	21 495	35
Other	0.8	n/a	<5
Non-Indigenous	0.5	5 368 180	84

*Includes Newfoundland and Labrador, Prince Edward Island, Nova Scotia and New Brunswick. Fewer than five cases reported so incidence rate not calculated.
†Canada and province/territory-specific populations are averaged from 2013 to 2016 StatsCan July 1 yearly population estimates. Indigenous Status-specific populations are taken from the 2016 StatsCan Census.

(n=28, 14%). Annual incidence rates by province or territory of residence and First Nation and Inuit status are shown in table 2. The highest rates were in Nunavut (80.6 cases per 100 000, greater than 80 times that of the rest of Canada combined) and Manitoba (8.5 cases per 100 000). Of the 70 children identified as First Nations, 64 (91%) had their residence on reserve.¹²

Results related to exposure and previous TB diagnosis are shown in table 3. A source case was identified in 73% of cases: most (n=91, 65%) were close household contacts of either a first-degree (48%) or second-degree (37%) relative. Twenty-five children (of whom 12 (48%) were First Nation and 9 (36%) were Inuit) had previously received TB treatment, chiefly for latent TB infection.

Selected clinical features are shown in table 4. TB was intrathoracic in 183 (92%) patients of whom 25 (14%) had extrathoracic involvement. The most common extrathoracic sites were the central nervous system (CNS) and peripheral lymph nodes. Miliary or disseminated disease was seen in 20 cases. Five (14%) cases in Inuit children involved the CNS, of whom 3 (60%) had received BCG vaccine. Approximately two-thirds had symptoms, most commonly cough fever and weight loss. Only 12 (6%) children with incident TB had the classic triad of cough, weight loss and night sweats and fewer than 5 children had haemoptysis.

One hundred and sixty-five children had at least one tuberculin skin test performed of which 144 (87%) were positive. An interferon gamma release assay test was performed in 13 children of whom 10 (77%) were positive. Overall, 80 (40%) children had at least one positive culture from any site. One hundred and forty-four children had at least one respiratory sample taken for mycobacterial culture; culture was positive in 31 of 77 (40%) sputum and 31 of 74 (42%) gastric aspirate samples; 55% of children with intrathoracic TB in whom a respiratory sample was obtained had negative cultures. Nineteen of 77 (25%) sputa

Table 3 Key exposure, epidemiologic and past tuberculosis history data

	Number (n)	%
Source case (N=198)		
Known	145	73
Unknown	53	27
Source case relationship (N=128)		
First-degree relative	62	48
Second-degree relative	47	37
Friend	11	9
Other	8	6
Exposure type (N=140)		
Close household	91	65
Close non-household	34	24
Casual	6	4
Visit to endemic country	7	5
Community/other	<5	n/a
Source case case known resistance to first-line agents* (N=137)		
Resistant	5	4
Not resistant	117	85
Not done or unknown	15	11
BCG vaccination (N=188)		
Yes†	86	46
No	81	43
Unknown	21	11
Previous tuberculosis diagnoses or treatment		
Latent tuberculosis, treated	17	8.5
Latent tuberculosis, untreated	<5	n/a
Active tuberculosis, treated	<5	n/a
Window prophylaxis	<5	n/a
Unspecified/unknown anti-tuberculosis therapy	<5	n/a

*All positive tuberculosis cultures in Canada undergo phenotypic drug-susceptibility testing. First-line agents are isoniazid, rifampin, pyrazinamide and ethambutol.
†For all children for whom immunisation status was known, BCG was received by 79% of Inuit children, 65% of First Nations children and 87% of foreign-born children.

were in those younger than 5 years; of these, fewer than 5 were culture positive.

Resistance to at least one drug was reported in 5 (7%) isolates. Most were resistant to isoniazid and rifampin and thus classified as multi-drug resistant. There were no proven cases of extensively-drug-resistant TB.

The median duration of treatment for all cases was 26 weeks (IQR 24–32), for TB meningitis 48 weeks (IQR 30–65) and for disseminated disease 48 weeks (IQR 40.5–54). Median duration of therapy for the five cases with documented resistance was 48 weeks (IQR 36–48). Most children were treated with a three-drug regimen of isoniazid, rifampicin and pyrazinamide (n=99, 50%) or four-drug regimen that included ethambutol (n=79, 40%). Use of directly observed therapy was reported in 183 (96%) cases for which this information was available.

Reported and minimum estimated rates of selected clinical events are shown in online supplemental table 1. Fifty-one per cent of children were admitted to hospital for a median of 14 days (IQR 7–19, maximum 252). Intensive care unit (ICU) admission status was known for 84 children of whom 11 (5.5%) required ICU level care. Seven (54%) children admitted to ICU had CNS involvement.

In 17 cases (9%), an ADR required a change in treatment and 6 cases required hospitalisation for the ADR. The most

Table 4 Selected clinical features and results of investigations

	Number (n), n (%)	Duration, median (IQR)
Disease site*		
Only intrathoracic	158 (81)	
Intrathoracic and extrathoracic	25 (13)	
Only extrathoracic	13 (7)	
Extrathoracic sites		
Central nervous system	16 (8)	
Peripheral lymph nodes	13 (7)	
Symptoms†		
Cough	84 (42)	28 days (14–30 days)
Fever	52 (26)	16 days (7–78 days)
Weight loss	36 (18)	
Haemoptysis	<5	
No recorded symptoms	65 (33)	
Tests of infection		
TST positive	144/165 (87)	
IGRA positive	10/13 (77)	
Positive TB culture		
Any site (one or more)	80/200 (40)	
Sputum	31/77 (40)	
Gastric aspirates	31/74 (42)	

* Four cases with incomplete data excluded from analysis of disease site.

† No data on presence or absence of symptoms for 18 cases.

IGRA, Interferon gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

common drugs implicated in ADR were pyrazinamide (5%, most commonly for hepatotoxicity) and isoniazid (3%, most commonly for hepatotoxicity). Other implicated drugs included amikacin (hearing loss), rifampicin (hepatotoxicity), ethambutol (visual changes), linezolid (marrow suppression) and cycloserine (neuropathy).

Longer term follow-up information was provided in 106 cases and of these, 97% and 90% had shown clinical and radiologic improvement, respectively, at the time of final follow-up. Sixteen cases reported an extension of therapy beyond the originally planned time frame. Most common reasons for extended treatment included poor adherence to therapy (n=5), extrathoracic site of infection found after initiation of therapy (<5), poor radiologic or clinical response (<5) and drug resistance (<5). Fewer than five cases were reported as lost to follow-up and there were no TB-related deaths.

To understand the representativeness of our cases, we compared our results to the numbers of cases reported to the PHAC during the study time frame. Cases are de-identified in both reporting systems and could not be matched. For 2014 and 2015, where reporting periods were identical, CPSP reports were 74% of all cases reported to PHAC and 90% of PHAC reported cases when the province of Québec was excluded (online supplemental table 2). During the study, there were significant TB outbreaks in Nunavik, Québec, an Inuit region where TB is managed by clinicians not included in the CPSP surveillance system.¹³ Using additional demographic data from the province of Québec via PHAC (online supplemental table 3), we estimated a maximum number of 269 cases of childhood TB in Canada over the study period.¹⁴ Using these data, the minimum national incidence rates were 10.2/100 000/year for all Indigenous children, 100.8/100 000/year for Inuit children and 1.55/100 000/year for all children in Canada (online supplemental table 4).

DISCUSSION

This study is one of the first nation-wide surveys to collect TB data directly from treating clinicians. The overall rate of reported cases of childhood TB in this study was 1.2 per 100 000. This compares with an approximate incidence of rate of 1.6/100 000 from PHAC data¹⁵ and 1.9 in the Netherlands,¹⁶ 2.0 in the UK¹⁷ and 0.7 per 100 000 in the USA.¹⁸

There was wide variation across Canada geographically and by population origin of the cases. The most striking finding is the burden of TB in Indigenous children. In 2016, Indigenous people comprised 19% of all reported TB cases in all ages.¹⁵ Though Indigenous children accounted for less than 10% of Canada's childhood population, 58% of reported TB was in this group. The rates in First Nations children (9.1 per 100 000 calculated from CPSP reported cases), especially those residing on reserve (20.2 per 100 000) are the drivers for childhood TB in the provinces of Manitoba, which had the greatest absolute number of cases, and Saskatchewan. The rate in Inuit children (54.3/100 000 population) is similar to reported childhood TB rates in high TB burden international settings.¹ Furthermore, when Québec cases not reported to CPSP are included, the minimum incidence rate in Inuit children is likely greater than 100/100 000 per year. Additionally, five cases from Newfoundland and Labrador where 90% of PHAC reported cases are Inuit were reported to PHAC but not to the CPSP.

In recognition of this hugely disproportionate burden in Inuit peoples, there has been a recent focus by the national representative organisation of Inuit peoples (Inuit Tapiriit Kanatami) and the Federal Government on social determinants of health and access to care as major contributors to TB in Inuit peoples¹⁸ and a pledge to reduce rates in Inuit Nunangat (the traditional territory of Inuit peoples in Canada) by 2030.¹⁹ A similar strategy and monitoring programme has been implemented by the Assembly of First Nations to focus on TB on First Nation reserves.¹⁹ The disproportionate burden of TB in Indigenous people in Canada has origins in the social determinants of health, historical trauma, the residential school system and racism within the healthcare system.²⁰ Reducing and eliminating TB in Indigenous communities through Indigenous-led and community-relevant approaches are the most urgent priorities for achieving elimination of childhood TB in Canada.

In keeping with other studies, most cases occurred in children under 5 years of age, reflecting the unique vulnerability of young children to TB.²¹ There was a known TB contact in 82% of Canadian-born children, reinforcing the importance of contact tracing and a public health infrastructure to diagnose and prevent TB in Canada. Only 18% of foreign-born children had a known contact; most of them likely acquired TB infection in the country of birth or by travel to a higher TB endemic country after arrival in Canada.

Presenting symptoms were non-specific but most children were symptomatic for more than 2 weeks. Haemoptysis and the classic triad of weight loss, fever and night sweats was uncommon. This study highlights acuity and health system costs of childhood TB. About half of children were hospitalised and 5.5% were known to be admitted to ICU. TB meningitis, a condition associated with poor outcomes²² was the most common extrapulmonary site occurring in 8% of cases overall and 14% of reported disease in Inuit children. Of the children with meningitis with known BCG status, 7 (54%) had received the BCG vaccine.

A strength of this study was inclusion of clinicians managing cases through a cross-Canada collaborative network. While monthly surveys of clinicians are labour-intensive, it is possible to obtain rich epidemiologic and clinical data that is not possible

through public health reporting. However, it has several limitations including voluntary reporting with some cases not captured. The largest discrepancy between the reported number of CPSP and PHAC cases was in Québec. Due to under-reporting, the representativeness of the acuity of cases cannot be confirmed, though minimum rates have been estimated. Follow-up data was less well reported than the initial incident case. Reasons for missing follow-up data included the reporting physician was not the physician who provided longer term care, the physician did not consent to being recontacted or the physician did not respond. Due to CPSP privacy rules, results with size <5 cannot be shown, which limits the description of rare outcomes. We captured region of residence and of diagnosis, however, these may not reflect the region of disease acquisition. We are not able to determine which cases were identified via a symptomatic child presenting to care versus via contact tracing nor were we able to determine clinical details of prior TB infection. Our surveillance asked only which drugs TB isolates were resistant to, not all drugs tested. The determination of TB acquired during travel used dates of travel to an endemic country, contact history and onset of disease, however, infection may have been acquired at another time. We recommend that future national surveillance and statistics about childhood TB should include detailed data about indigenous status, source case characteristics, prior infection and travel.

CONCLUSION

This surveillance study identified 200 incident cases of childhood TB over 3 years. Acuity of illness and resource utilisation were high. Most cases had a known source case. Outbreaks of childhood TB in low TB burden countries are best prevented by prompt identification of source cases, and evaluation and treatment of their contacts and require a well-functioning public health infrastructure and good contact tracing. Key geographies and groups have very high incidence rates of childhood TB that are comparable with highly endemic countries. Strong community and public health engagement are required to reduce disparities and achieve elimination of childhood TB in Canada.

Author affiliations

- ¹Infectious Diseases, The Hospital for Sick Children, Toronto, Ontario, Canada
- ²University of Toronto, Toronto, Ontario, Canada
- ³The Hospital for Sick Children, Toronto, Ontario, Canada
- ⁴University of Manitoba, Winnipeg, Manitoba, Canada
- ⁵Saskatchewan Infectious Disease Care Network, Saskatoon, Saskatchewan, Canada
- ⁶Government of Nunavut, Iqaluit, Nunavut, Canada
- ⁷Pediatric Infectious Diseases, CHU Sainte-Justine, Montreal, Quebec, Canada
- ⁸Division of Respiratory Medicine, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada
- ⁹University of Alberta, Edmonton, Alberta, Canada
- ¹⁰Alberta Health Services, Edmonton, Alberta, Canada
- ¹¹British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada
- ¹²The University of British Columbia, Vancouver, British Columbia, Canada
- ¹³University of Calgary, Calgary, Alberta, Canada
- ¹⁴London Health Sciences Centre Children's Hospital, London, Ontario, Canada
- ¹⁵Public Health Agency of Canada, Ottawa, Ontario, Canada
- ¹⁶Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
- ¹⁷British Columbia Women's Hospital and Health Centre, Vancouver, British Columbia, Canada
- ¹⁸Children's Hosp Eastern Ontario, Ottawa, Ontario, Canada
- ¹⁹Qikiqtani General Hospital, Iqaluit, Nunavut, Canada
- ²⁰Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
- ²¹University of Ottawa, Ottawa, Ontario, Canada
- ²²Saskatchewan Health Authority, Saskatoon, Saskatchewan, Canada
- ²³University of Saskatchewan, Saskatoon, Saskatchewan, Canada
- ²⁴Health Canada, Ottawa, Ontario, Canada
- ²⁵Dalhousie University, Halifax, Nova Scotia, Canada
- ²⁶IWK Health Centre, Halifax, Nova Scotia, Canada

²⁷Stanton Territorial Hospital, Yellowknife, Northwest Territories, Canada

²⁸Toronto Public Health, Toronto, Ontario, Canada

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Competing interests JML holds the CIHR-GSK Chair in Pediatric Vaccinology at Dalhousie University.

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ORCID iDs

Shaun K Morris <http://orcid.org/0000-0001-9809-0822>

Jeffrey M Pernica <http://orcid.org/0000-0002-4380-5402>

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