

Pediatric Tuberculosis in Alberta

Epidemiology and Case Characteristics (1990-2004)

David Yip, MD, MPH^{1,2}

Ravi Bhargava, MD¹

Yin Yao, PhD²

Karen Sutherland, MA^{1,3}

Jure Manfreda, MD, MSc⁴

Richard Long, MD^{1,3}

ABSTRACT

Background: Pediatric tuberculosis (TB) is important medically and indicative of a public health problem. An understanding of the epidemiology and case characteristics of pediatric TB, in a province that accepts large numbers of immigrants, can inform TB elimination strategy.

Methods: All cases of pediatric TB notified in Alberta between 1990 and 2004 were identified in the TB Registry. Individual diagnostic criteria were reviewed and case patients were related to a population grid derived from Statistics Canada censuses and population estimates of Status Indians from the Department of Indian and Northern Affairs, Canada. Incidence rates were determined by ethnic group and gender. Clinical/mycobacteriologic case characteristics were compared by ethnic group and birth country.

Results: Among 124 notified cases, 95 (96 episodes) met strict diagnostic criteria: 45 Status Indians, 30 Canadian-born 'other' and 21 foreign-born. Incidence rates were much higher in Status Indians and the foreign-born compared to the Canadian-born 'other'; 10.7, 5.4, and 0.4 per 100,000 person-years, respectively. Among Canadian-born 'other' cases, 12 were Métis and 11 were Canadian-born children of foreign-born parents. Compared to foreign-born cases, Canadian-born cases were more likely to have a source case in Alberta, to be detected through contact tracing, to have primary pulmonary TB, and to have a rural address.

Conclusion: Pediatric TB in Alberta is mainly the result of ongoing transmission in Aboriginal peoples and immigration to Canada of persons with latent TB infection. The elimination of pediatric TB will require interruption of transmission in Aboriginal peoples and prevention of disease in immigrants.

MeSH terms: Pediatric; tuberculosis

La traduction du résumé se trouve à la fin de l'article.

1. Department of Medicine and Radiology, University of Alberta, Edmonton, AB

2. Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland

3. Disease Control and Prevention Branch, Alberta Health and Wellness

4. Department of Community Health Sciences, University of Manitoba, Winnipeg, MB

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Correspondence and reprint requests: Dr. Richard Long, Tuberculosis Program Evaluation and Research Unit, Room 8325, Aberhart Centre 1, 11402 University Avenue, Edmonton, AB T6G 2J3, Tel: 780-407-1427, Fax: 780-407-1429, E-mail: richard.long@ualberta.ca

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Pediatric tuberculosis (TB) is important medically and indicative of a public health problem, yet there have been no comprehensive epidemiologic studies of the disease in Canada. Children are at increased risk of severe forms of TB such as central nervous system (CNS) and disseminated disease. TB in children usually reflects recent transmission from an infectious adult; the interruption of transmission is a necessary condition of TB elimination.¹⁻⁶

Both Canada and the United States now report the majority of their TB cases in the foreign-born.^{7,8} In Canada, most foreign-born TB cases are reported in the major immigrant-receiving provinces of Ontario, British Columbia, Quebec and Alberta.⁷ In Alberta, TB rate estimates that accommodate the variable in-Canada person-years of the foreign-born, have been reported for 1989 to 1998.⁹ The highest rates and highest proportion of cases were reported in foreign-born persons arriving from Asia. Similar high rates, but a lower proportion of cases, were reported in Status Indians, a subset of the Canadian-born population that is legally recognized by the federal government to be "Indian" for the purposes of the *Indian Act*.

In this study, we extended our earlier work and focused upon pediatric TB, defined as TB in persons less than 15 years of age. We examined the period 1990 to 2004, when Canada and Alberta were experiencing sustained high immigration. We applied a strict case definition to each notified case and determined incidence rates from a derived population grid. Rates were compared by gender and ethnic group. Clinical/mycobacteriologic case characteristics were compared by ethnic group and birth country.

METHODS

Children less than 15 years of age, who had been notified with TB during the 15-year period from 1990 to 2004, were identified in the Alberta TB Registry. The disease status of each notified case was re-evaluated after careful review of diagnostic data. This review included the study of individual case records maintained by Alberta Health and Wellness, TB Clinics (Calgary and Edmonton), and hospitals, as appropriate. Each child's mycobacteriologic test results were reassessed by review of

records maintained by the Laboratory for Public Health where all mycobacteriology in the province is performed. Each child's chest radiographs and/or other available radiologic studies were re-assembled and re-reported by a pediatric chest radiologist (RB). The diagnosis of TB, when not based upon a positive culture of *Mycobacterium tuberculosis*, was based upon all of the following criteria being present: 1) a history of contact with a source case and/or a positive tuberculin skin test (TST), 2) a chest radiologic abnormality consistent with disease if pulmonary,¹⁰ a clinical and/or radiologic picture consistent with disease if non-pulmonary (in some instances, clinical and/or radiologic findings were supported by pathologic findings), 3) a consistent clinical and radiologic response to treatment and 4) a completed diagnostic work-up. TSTs were performed by the Mantoux method, using 5 TU of PPD, and interpreted in accordance with the Canadian TB Standards.¹¹

Case patients were described according to ethnicity (Status Indians, Canadian-born 'other' and foreign-born). Canadian-born 'other' case patients were further described as non-Status Indian, Métis or Inuit or Canadian-born non-Aboriginal children of foreign-born or Canadian-born parents. Non-Status Indian, Métis and Inuit cases were grouped with the Canadian-born 'others' as population estimates in these groups are imprecise.

Incidence rates were calculated from population estimates derived from Statistics Canada censuses conducted in 1986, 1991, 1996 and 2001 and population estimates of Status Indians provided by the Department of Indian and Northern Affairs, Canada. Inter-censal estimates were calculated using linear interpolations between censuses. Estimates from 2002-2004 were obtained by linear extrapolation.

Case patients were described according to age, gender, method of detection (symptoms, contact tracing, screening), identification of a source case in Alberta, disease site, bacillary status, and place of residence at diagnosis (metropolitan area [Calgary or Edmonton] versus rural). TB outcomes were reported as: survived/died, treatment complete/incomplete, severe disease/no severe disease.

TABLE I
Pediatric Tuberculosis Case Rates in Alberta by Ethnic Group and Gender, 1990-2004

Ethnic Group	Gender	Person-years (in 100,000)	Cases	Crude Rate*	95% CI
Status Indian	Male	2.1	23	10.74	6.4-15.1
	Female	2.0	22	10.75	6.2-15.2
	Total	4.2	45	10.74	7.6-13.9
Canadian-born 'Other'	Male	42.5	10	0.24	0.1-0.4
	Female	40.4	20	0.50	0.3-0.7
	Total	82.9	30	0.36	0.2-0.5
Foreign-born	Male	2.0	8	4.01	1.2-6.8
	Female	1.9	13	6.77	3.1-10.5
	Total	3.9	21	5.37	3.1-7.7
All Ethnic Groups	Male	46.7	41	0.9	0.6-1.2
	Female	44.4	55	1.2	0.9-1.2
	Total	91.0	96	1.1	0.8-1.3

* Rate estimates are per 100,000 person-years

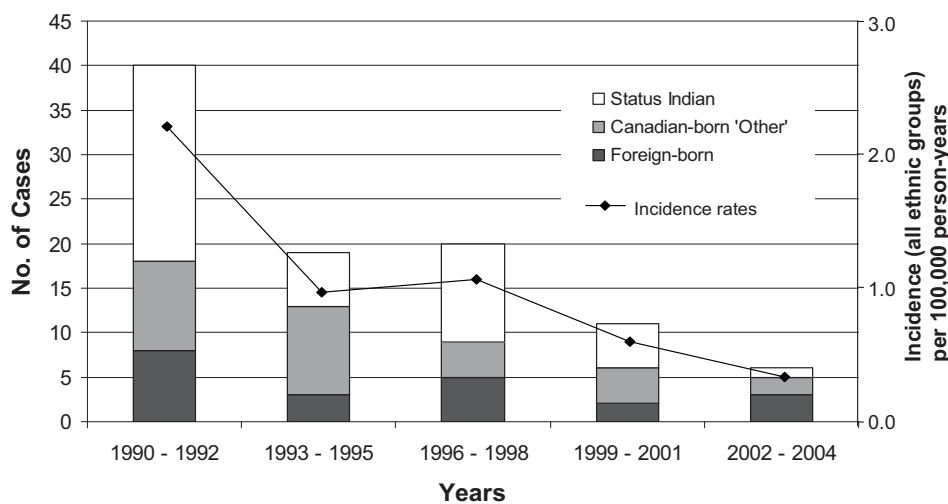


Figure 1. Pediatric TB in Alberta by ethnic group (1990-2004)

Statistical methods

Multivariate Poisson regression was used to determine the association of gender and ethnicity with TB rates. Chi-square was used to test the differences in the proportion of TB cases between ethnic group and birth country. If the expected frequencies were less than 5, Fisher's exact test was used instead of the Chi-square test. Two-independent sample t-test was used to test the difference in the mean ages between Canadian-born and foreign-born. The study was approved by the Health Research Ethics Board of the University of Alberta.

RESULTS

Over the 15-year period from 1990-2004, 124 children aged <15 years were notified in the Alberta Health & Wellness TB Registry; 6 other children were notified in Alberta but should properly have been notified elsewhere; 4 foreign-born children were diagnosed and received their initial

phase of treatment overseas; 2 Status Indians were referred for diagnosis from other provincial/territorial jurisdictions. Of the 124 notified Alberta cases, 29 (23.4%) did not meet strict diagnostic criteria; 24 culture-negative "primary pulmonary" cases had normal chest radiographs (14 Status Indians, 8 Canadian-born 'other', and 2 foreign-born), and 5 culture-negative non-pulmonary cases had inconclusive biopsies and/or other investigations (2 Status Indians, 1 Canadian-born 'other', and 2 foreign-born). Errors in radiograph reporting were related to inexperience, the absence of lateral projections, and a failure to integrate information from serial films. All 95 patients had new active disease. One foreign-born patient had both a new active and a relapse episode, separated in time by 14.5 months of inactivity. Forty-five episodes occurred in Status Indians, 30 in Canadian-born 'other' (12 Métis, 11 Canadian-born non-Aboriginal children of foreign-born parents, and 7 Canadian-born non-Aboriginal children of

TABLE II
Characteristics of Pediatric TB Cases in Alberta by Ethnic Group and Country of Birth, 1990-2004

Characteristic	Total No. (%) *	Status Indian No. (%)	Canadian-born	Foreign- born No. (%)	p value†
			Other No. (%) [Canadian-born No. (%)]		
Number Assessed	96 (100)	45 (46.9)	30 (31.3) [75 (78.1)]	21 (21.9)	
Age (years)					
<5	44 (45.8)	19 (42.2)	20 (67.7) [39 (52.0)]	5 (23.8)	<0.05
5-14	52 (54.2)	26 (57.8)	10 (33.3) [36 (48.0)]	16 (76.2)	<0.05
Sex					
Male	41 (42.7)	23 (51.1)	10 (33.3) [33 (44.0)]	8 (38.1)	>0.05
Female	55 (57.3)	22 (48.9)	20 (67.7) [42 (56.0)]	13 (61.9)	>0.05
Method of Detection					
Symptoms	24 (25.0)	2 (4.4)	8 (26.7) [10 (13.3)]	14 (67.7)	<0.05
Contact tracing	72 (75.0)	43 (95.6)	22 (73.3) [65 (86.7)]	7 (33.3)	<0.001
Source Case					
Known (Alberta)	77 (80.2)	45 (100.0)	24 (80.0) [69 (92.0)]	8 (38.1)	<0.01
Unknown	19 (19.8)	0 (0.0)	6 (20.0) [6 (8.0)]	13 (61.9)	<0.001
Culture Status					
Positive	36 (37.5)	16 (35.6)	9 (30.0) [25 (33.3)]	11 (52.4)	>0.05
Negative‡	60 (62.5)	29 (54.4)	21 (70.0) [50 (66.7)]	10 (47.6)	>0.05
Disease Site					
Primary pulmonary	77 (80.2)	45 (100.0)	22 (73.3) [67 (88.2)]	10 (47.6)	<0.001
Other	19 (19.8)	0 (0.0)	8 (26.7) [8 (11.8)]	11 (52.4)	<0.001
Place of Residence					
Metropolitan§	32 (33.3)	1 (2.2)	14 (46.7) [15 (20.0)]	17 (81.0)	<0.001
Rural	64 (66.7)	44 (97.8)	16 (53.3) [60 (80.0)]	4 (19.0)	<0.001

* 96 episodes; 95 cases

† The first row of p values refers to a comparison of Status Indians with Canadian-born 'others', the second row to a comparison of Canadian-born to foreign-born.

‡ One culture-negative, Canadian-born child of foreign-born parents did not have a positive TST or a known source case. The diagnosis was based upon clinical and pathologic data.

§ Metropolitan area = Calgary or Edmonton

Canadian-born parents) and 21 in foreign-born.

The overall rate of pediatric TB in Alberta was 1.1 per 100,000 person-years. In the multivariate Poisson regression, Status Indians and the foreign-born had significantly higher rates of TB in comparison to the Canadian-born 'other' [Status Indians: rate ratio (RR) = 29.69, 95% CI: 18.71-47.12, $p < 0.001$; and foreign-born: RR = 14.82, 95% CI: 8.49-25.89, $p < 0.001$] after controlling for gender (Table I). Males had increased risk of TB in comparison to females but the differences in the risk were not statistically significant [RR = 1.40, 95% CI: 0.94-2.10, $p = 0.1$]. The interaction between ethnicity and gender was not statistically significant in the Poisson regression. Case rates fell over time (see Figure 1), perhaps because

there were fewer source cases in the population, or perhaps because of the timing and size of Status Indian outbreaks: 1992 (18 children), 1993 (3 children), 1998 (13 children).¹²

The characteristics of the cases are described in Table II by ethnic group and country of birth. The median age of cases was 5 years. Status Indians were more likely than Canadian-born 'others' and Canadian-born were more likely than foreign-born to have a source case in Alberta, to be detected through contact tracing, to have primary pulmonary TB, and to have a rural address at diagnosis. Compared to foreign-born cases, Canadian-born cases were younger (mean age [\pm SD] 5.1 \pm 4.2 vs. 9.8 \pm 4.5 years, $p < 0.001$). Among culture-positive foreign-born cases, 8 (72.7%) had no source case in Alberta. Three initial

isolates were streptomycin mono-resistant; two were from foreign-born children (no Alberta source case), one was from a Canadian-born child of foreign-born parents (Alberta source case streptomycin-resistant). Most foreign-born cases (90.5%) and foreign-born parents of Canadian-born cases (100.0%) were born in a 'high incidence' country, defined as a country whose average World Health Organization reported incidence of smear-positive pulmonary TB over the past 3 years was ≥ 15 cases per 100,000 persons.¹³ The median length of stay in Canada of foreign-born cases, prior to diagnosis, was 26 months (range 3 to 179 months).

Of the 95 cases (96 episodes), one child – a Métis – died of congenital TB. All of the remaining children survived and completed treatment. Three children had CNS TB (1 Status Indian, and 2 Canadian-born non-Aboriginal children, one of Canadian-born parents and the other of foreign-born parents) and 1 child had disseminated TB (a Canadian-born non-Aboriginal child of foreign-born parents). All but 1 of the above 5 children were <5 years of age at diagnosis. None were known to be HIV co-infected and none had received BCG vaccination. (BCG was only offered to Canadian-born children who were Status Indian and born into reserve communities; 11 of 45 Status Indian cases received BCG. Many foreign-born cases are presumed to have received BCG but their vaccination histories are undocumented).

DISCUSSION

The diagnosis of TB in children can be difficult. They often have non-specific signs and symptoms and a paucity of mycobacteria.¹⁻³ In this study, as in an earlier study of on-reserve Status Indian children,¹² we found that a significant proportion of cases notified to the province did not meet strict criteria for the diagnosis. The majority of these non-cases had been diagnosed with primary pulmonary TB, yet in hindsight their radiographs were normal and their cultures were negative. If specimens for TB smear and culture are not submitted, or if submitted are not positive, then one must rely upon a clinical case definition to distinguish disease, from infection without disease.¹⁻³ For cases of bacillary-negative primary pulmonary TB, the chest radi-

ograph ought to be abnormal.¹⁴ To optimize the chances of discerning intrathoracic adenopathy, both posterior-anterior (PA) and lateral chest radiographs are recommended.^{15,16} Expert radiologic opinion is also recommended. When PA and lateral chest radiographs are read by primary care physicians or pediatricians, and CT thorax is used as the reference standard, the sensitivity and specificity for adenopathy is only 68.1% and 63.6%, respectively.¹⁷ In our study, presenting and follow-up films were re-read by an experienced pediatric chest radiologist. Our non-cases might have been considered "provider-diagnosed" cases by some, having been treated as TB at the time.^{2,5,18} However, the criteria for a "provider-diagnosed" case are non-uniform and, in our opinion, untenable in the presence of a normal chest radiograph.^{18,19} In the United States between 1993 and 2001, 23% of cases were "provider-diagnosed".⁵

Using a strict numerator (case definition) and denominator (populations in person-years), we found the overall pediatric TB rate estimate to be low in Alberta. There were, however, remarkable differences between ethnic groups. Rate estimates in the Status Indians and foreign-born were about 30 times and 15 times higher, respectively, than the rate estimates in the Canadian-born 'other'. These rate estimates paralleled those seen in 1989-1998 when all age groups in Alberta were included.⁹ In 1989-1998, the all-age TB disease burden was highest in the foreign-born (56.3% of cases); in 1990-2004, the child-age TB disease burden was highest in the Status Indians (46.9% of cases) with only 21.9% of cases in the foreign-born. That Status Indian children had the highest rate and burden of TB is consistent with data on TB transmission in Alberta. Compared to Canadian-born 'others' and the foreign-born, Status Indians had significantly higher transmission indices, determined by calculating the average number of culture-positive pulmonary cases generated by a single source case.²⁰ Early detection of source cases and thorough contact tracing are critical to TB control in Status Indians.^{21,22} Many Status Indian cases occurred in outbreaks. Their treatment outcomes were much improved over the pre-antibiotic era.²³

As the number of cases in Aboriginal peoples fall, the proportion of all cases that

are occurring in the foreign-born, or in Canadian-born children of foreign-born parents, is expected to rise. Among cases that were not Status Indian or Métis, 82.1% were either foreign-born or Canadian-born children of foreign-born parents. The importance of screening child-aged contacts of foreign-born cases has been emphasized in the Netherlands.²⁴ Exposure of newborns to foreign-born source cases has been reported in Neonatal Intensive Care Units in Canada.^{25,26} Most foreign-born cases and foreign-born parents of Canadian-born cases were born in high-incidence countries (90.5% and 100.0%, respectively).¹³

There were also remarkable differences in the clinical and mycobacteriologic characteristics of pediatric cases by ethnic group and birth country. Status Indians were more likely than Canadian-born 'others' and Canadian-born were more likely than foreign-born, to be younger, to have a source case in Alberta, to be detected through contact tracing, and to have primary pulmonary TB. Foreign-born cases with no identified source case in Alberta were presumed to have acquired their infection overseas. As such, their incident case is not a local, sentinel event; it might have been a preventable event had latent TB infection (LTBI) been detected upon arrival.^{6,27-29} When adult source case and pediatric contact are culture-positive, there is a high degree of concordance in their drug susceptibility test results.³⁰ When there is no source case and the pediatric case is culture-negative, then epidemiologic circumstances must be taken into account when prescribing anti-tuberculosis drugs.³¹ In Canada, foreign birth is a significant predictor of drug-resistant TB.³² Accordingly, a special effort must be made to recover the organism from foreign-born children suspected of having TB but lacking an in-Canada source case – in respiratory cases, three or more sputum or gastric aspirate specimens; in non-respiratory cases, one or more specimens appropriate to the site of disease.

In contrast to the USA, where the majority of cases were reported from metropolitan areas,⁵ the majority of Alberta cases were reported from rural areas. Among Canadian-born cases that were not born of foreign-born parents, 85.9% were of Aboriginal ancestry and living in a rural

area at diagnosis. Among foreign-born cases or Canadian-born cases of foreign-born parents, 90.6% were living in a metropolitan area at diagnosis.

In conclusion, pediatric TB in Alberta is mainly the result of ongoing transmission in Aboriginal peoples, and immigration to Canada of persons with LTBI. The elimination of pediatric TB will require interruption of transmission in Aboriginal peoples and prevention of disease in immigrants.

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RÉSUMÉ

Contexte : Outre son importance sur le plan médical, la tuberculose infantile est l'indicateur d'un problème de santé publique. La connaissance de l'épidémiologie et des caractéristiques des cas de tuberculose infantile en Alberta, une province qui accueille des immigrants en grand nombre, pourrait étayer la stratégie d'élimination de la tuberculose.

Méthode : Nous avons relevé dans le registre de la tuberculose tous les cas de tuberculose infantile déclarés en Alberta entre 1990 et 2004. Les critères de diagnostic de chaque cas ont été examinés, et les cas déclarés ont été reportés sur une grille démographique dérivée des recensements de Statistique Canada et des estimations de la population des Indiens de plein droit du ministère fédéral des Affaires indiennes et du Nord. Des taux de fréquence ont été calculés par groupe ethnique et par sexe. Les aspects cliniques et mycobactériologiques de chaque cas ont été comparés selon le groupe ethnique et le pays d'origine.

Résultats : Sur les 124 cas déclarés, 95 cas (soit 96 accès de tuberculose) répondaient strictement aux critères de diagnostic : 45 Indiens de plein droit, 30 « autres » sujets nés au Canada et 21 sujets nés à l'étranger. Les taux de fréquence étaient beaucoup plus élevés chez les Indiens de plein droit et les sujets nés à l'étranger que chez les « autres » sujets nés au Canada (soit 10,7, 5,4 et 0,4 pour 100 000 personnes-année, respectivement). Chez les « autres » sujets nés au Canada, 12 étaient des Métis et 11 étaient des enfants nés au Canada de parents étrangers. Par rapport aux cas de tuberculose infantile chez les sujets nés à l'étranger, les cas répertoriés chez les sujets nés au Canada étaient plus susceptibles d'avoir un cas source situé en Alberta, d'avoir été détectés par recherche de contacts, de présenter une tuberculose pulmonaire primaire et d'avoir une adresse rurale.

Conclusion : La tuberculose infantile en Alberta résulte principalement de la transmission continue du virus dans la population autochtone et de l'immigration au Canada de personnes atteintes de tuberculose latente. L'élimination de la tuberculose infantile nécessite donc à la fois l'interruption de la transmission du virus chez les Autochtones et la prévention de l'évolution de la maladie chez les immigrants.