

Pediatric Tuberculosis in Alberta First Nations (1991-2000)

Outbreaks and the Protective Effect of Bacille Calmette-Guérin (BCG) Vaccine

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ABSTRACT

Background: The tuberculosis control strategy of vaccinating First Nations newborns with BCG (bacille Calmette-Guérin) is currently undergoing re-evaluation in Canada. Review of recent pediatric tuberculosis morbidity could inform this re-evaluation.

Methods: Potential source cases and pediatric cases of tuberculosis from Alberta First Nations were identified over the 10 years 1991-2000. The distribution of pediatric disease was described. The effect of BCG on tuberculosis morbidity in two large outbreaks was determined.

Results: A total of 57 potential source cases and 41 pediatric cases of tuberculosis were reported from 17 (41.5%) and 8 (19.5%) of the 41 on-reserve First Nation Community Health Centres, respectively. Three outbreaks traceable to three source cases accounted for 34 (18, 3, and 13, respectively) of the 41 (82.9%) pediatric cases. Each outbreak was spatially and temporally separate from the other. Each outbreak strain of *Mycobacterium tuberculosis* had a unique DNA fingerprint. In the largest outbreaks, disease-to-infection ratios (secondary case rates) were higher in newly infected unvaccinated versus vaccinated close pediatric contacts (12/13 [92.3%] versus 7/15 [46.7%], $p=0.02$), but the infection rate was almost certainly falsely high in the BCG vaccinated. One unvaccinated child had a brain tuberculoma in addition to primary pulmonary tuberculosis.

Conclusion: For most Alberta First Nations communities, the spatial and temporal distribution of disease, and the meager impact on morbidity, challenge the rationale for continued use of BCG.

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

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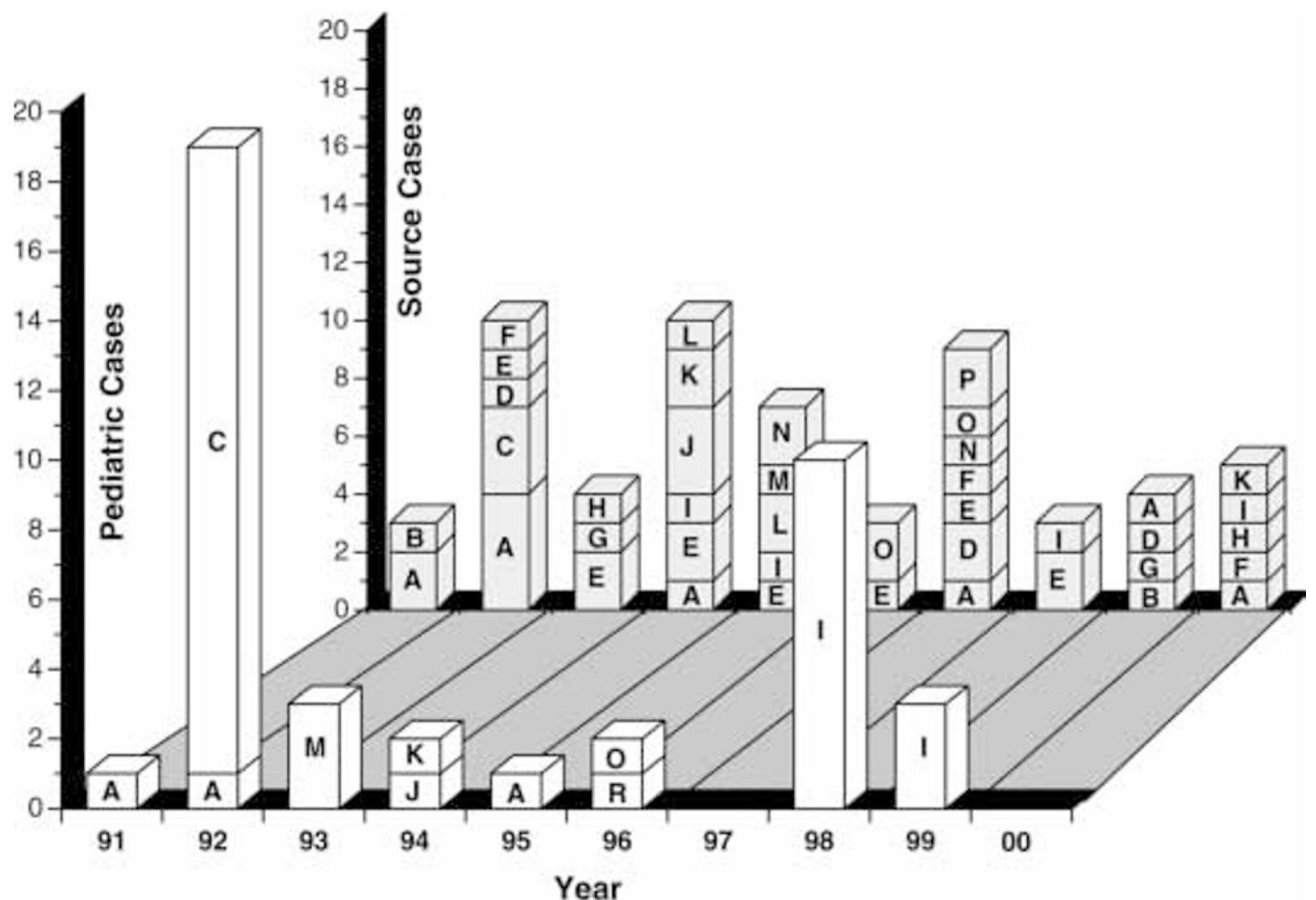
In the Province of Alberta, age-adjusted tuberculosis rates in Treaty First Nations are approximately 30 times higher than rates in the Canadian-born non-Treaty.¹ Within First Nations communities, tuberculosis cases in children represent ongoing transmission and at least a partial failure of the current tuberculosis control strategy. In this paper, we examine the occurrence of pediatric tuberculosis in the Alberta First Nations with a view to understanding what influence BCG (Bacille Calmette-Guérin) vaccination had on the burden of disease and its severity.

BCG is a live, attenuated vaccine derived from *Mycobacterium bovis*. Its administration to newborns is aimed at reducing the incidence and severity of tuberculosis among those born into endemic communities and where the diagnosis of tuberculosis may be delayed.^{2,3} Currently in Canada, BCG is offered to Inuit and on-reserve First Nations children born to mothers who tested negative for HIV prenatally. However, this policy is currently undergoing re-evaluation following reports of disseminated BCG in children born with congenital immunodeficiencies,^{4,5} and uncertainty about the indications for the vaccine.⁶ In Alberta, BCG was first introduced in 1948.⁷ Vaccination was never obligatory and current acceptance is far from universal.

METHODS

All potential source cases (persons > 14 years of age with smear-positive respiratory tuberculosis) and all pediatric cases (persons ≤ 14 years of age with tuberculosis of any disease type) reported from on-reserve First Nation Community Health Centres over the 10 years 1991-2000, were identified in the Alberta tuberculosis registry (Alberta Health and Wellness).

The case records, mycobacteriology and chest radiographs of the pediatric cases were reviewed to confirm their residence in a reserve community and their disease status. The diagnosis, when not based upon a positive culture, was based upon a history of contact with a source case, a newly positive tuberculin skin test (TST) or tuberculin conversion, a chest radiographic abnormality consistent with disease activity, and the clinical and radiographic response to treatment. Information concerning TST status, disease type, treatment



Community	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
Potential Source Cases/Population	8/8933	2/1036	3/2785	3/308	10/2924	3/548	2/1296	2/1138	5/716	3/2278	3/3219	3/560	1/2114	3/1724	3/7319	2/5668	1/886	0/644

Figure 1. Pediatric cases and source cases by community and year (1991-2000)
 The number of potential source cases (shaded blocks, background) and pediatric cases (open blocks, foreground) reported from on-reserve communities between 1991 and 2000 are displayed according to the community (letters) from which they were reported and the year in which they were reported. The populations (Department of Indian and Northern Affairs, 2000) of potential source case communities are listed; communities B and I included the reserve and an immediately adjacent off-reserve population (Statistics Canada, 2001).

and outcome was abstracted from individual medical records (Alberta Health and Wellness and University of Alberta). Tuberculin tests had been performed by the Mantoux method using 5TU of intermediate strength PPD.⁸ Tuberculin conversion was defined according to the *Canadian Tuberculosis Standards*.⁸ The BCG status (freeze-dried BCG, Connaught Laboratories) of cases and close contacts (see below) was determined by review of Community Health Centre records. Chest radiographs were interpreted systematically⁹ by a pediatric chest radiologist (RB), blind to the BCG status of the child.

When ≥ 3 epidemiologically linked pediatric cases were reported from the same community in 12 months, an outbreak was considered to have occurred. An outbreak was considered a micro-epidemic when it included ≥ 6 pediatric cases from ≥ 2 families.¹⁰ Micro-epidemics were described in detail. Routine laboratory methods were used.¹¹

Within each micro-epidemic, the source case contacts were identified from master contact lists maintained by Alberta Health and Wellness. Close contacts were defined as those living in the same household as the source case or those who, while not living in the same household, had regular

prolonged contact and daily shared breathing space with the source case.¹⁰ Contacts were divided into adult and pediatric, and close and not close (“other”). Close pediatric contacts were further divided into those who had or had not received BCG vaccination and those ≤ 5 years and > 5 years of age.

The “infection rate” was defined as the proportion of close pediatric contacts, with no record of a prior positive TST, who had a newly positive TST or a TST conversion. TST induration of ≥ 5 mm was considered positive.⁸ The “disease-to-infection ratio” was defined as the ratio of the newly TST positive or TST converting pediatric close

TABLE I
General Characteristics of Tuberculosis Micro-Epidemics in Alberta*

Characteristic		Micro-epidemic		
		Community C	Community I	Community C and I
No. of 'Close' Contacts*	Adult	53	42	95
	Pediatric	32	27	59
	Total	85	69	154
No. of 'Other' Contacts*	Adult	600	294	894
	Pediatric	493	129	622
	Total	1093	423	1516
No. of Cases†	Adult	15	14	29
	Pediatric	18	13	31
	Total	33	27	60
No. of Culture-positive Cases‡	Adult	8	9	17
	Pediatric	10	2	12
	Total	18	11	29
No. of Adult Cases Among Adult Contacts	'Close'	3	3	6
	'Other'	11	10	21
	Total	14	13	27
No. of Pediatric Cases Among Pediatric Contacts	'Close'	12	8	20
	'Other'	6	5	11
	Total	18	13	31

* definitions: 'close' contacts are defined in the text; 'other' contacts include casual and community contacts who are defined as those who spend time regularly but less frequently with the source case, and those who have infrequent, occasional contact with the source case, respectively.¹¹

† adult cases include the source cases

‡ within micro-epidemics, each isolate was DNA fingerprint identical; between micro-epidemics, each isolate was DNA non-identical

contacts that were secondary cases, to newly TST positive or TST converting pediatric close contacts that were not secondary cases. Infection rates and disease-to-infection ratios were compared in BCG vaccinated and unvaccinated children using the Chi-Square or Fisher's Exact Test.

RESULTS

A total of 57 potential source cases were reported from 17 (41.5%) and a total of 41 pediatric cases were reported from 8 (19.5%), of the 41 on-reserve First Nation Community Health Centres in Alberta over the 10-year period 1991-2000 (Figure 1). Fifteen other on-reserve First Nation children were diagnosed with suspect active tuberculosis and completed full courses of treatment. In retrospect, none of these children met diagnostic criteria for disease.

Of the 41 pediatric cases, 37 (90.2%) were linked to 8 (14.0%) of the 57 potential source cases. The 4 pediatric cases reported from communities M and R were linked to potential source cases living in nearby off-reserve communities. The pediatric cases reported from community A in

1991, 1992 and 1995 followed exposure to three different source cases. The pediatric cases reported from Community C in 1992 were judged to be secondary to one of three potential source cases. Source and pediatric case linkage was by both conventional and molecular epidemiology. Spatially and temporally separate micro-epidemics (communities C and I), and one small outbreak (community M), accounted for 34/41 (82.9%) of the pediatric cases. Among pediatric cases that were not part of a micro-epidemic, 1 had been BCG vaccinated and none developed CNS or disseminated tuberculosis.

The micro-epidemics occurred in relatively remote northern communities of unrelated First Nations. In community C, the source case was a 22-year-old postpartum female who lived in a house with more than 25 inhabitants. Many people shared the same house as not all houses were adequately heated. She reported a six-week history of productive cough and weight loss. She had been vaccinated with BCG at age seven. In community I, the source case was a 28-year-old male who had begun working as a teacher's aide in the local school (kindergarten to grade 9) approximately 4-6 weeks prior to diagno-

sis. He reported a 4-month history of productive cough and a 6-week history of weight loss. He had a remote past history of culture-positive primary pulmonary tuberculosis which was understood to have been adequately treated. Neither patient was HIV positive or otherwise co-morbid. Chest radiographs demonstrated bilateral far advanced and moderately advanced cavitory disease, respectively.¹² Sputum from both contained large numbers of acid-fast bacilli (AFB) and grew drug-susceptible *Mycobacterium tuberculosis*. Source cases were immediately placed in respiratory isolation.

Of 154 close contacts of the source cases, 59 (38.3%) were pediatric (Table I). Of the secondary cases in community C and I, 18/32 (56.3%) and 13/26 (50.0%), respectively, were pediatric. Secondary cases were much more likely to occur among "close" pediatric contacts (20/59 or 33.9%) than "other" pediatric contacts (11/622 or 1.8%), $p < 0.001$.

The mean (SD) age (7.3 ± 4.7 vs. 6.0 ± 3.9 years) and age distribution (< 1 to 14 vs. < 1 to 12 years) of the pediatric cases in community C and I were similar. BCG had been given to 1/18 (6%) community C and 10/13 (77%) community I pediatric cases. *M. tuberculosis* was less likely to be cultured from pediatric cases who were BCG vaccinated than those who were BCG unvaccinated (18% vs. 50%), though the average number of diagnostic specimens (airway secretions or lung tissue) submitted from cases in both groups was similar (3.1 ± 1.5 vs. 3.1 ± 1.4). Intrathoracic adenopathy was seen on chest radiograph in 7/11 (64%) BCG-vaccinated and 19/20 (95%) BCG-unvaccinated pediatric cases. One case, a 7-year-old BCG-unvaccinated child from community C, had a brain tuberculoma in addition to primary pulmonary tuberculosis. All pediatric cases survived and completed a satisfactory course of treatment. The child with the brain tuberculoma suffered no permanent neurologic deficit.

The infection rate and the disease-to-infection ratio among close pediatric contacts of the micro-epidemic source cases are derived from the screening outcomes displayed in Figure 2. One BCG-vaccinated contact in community I had been TST positive in the remote past. She developed TB disease. Three BCG-unvaccinated con-

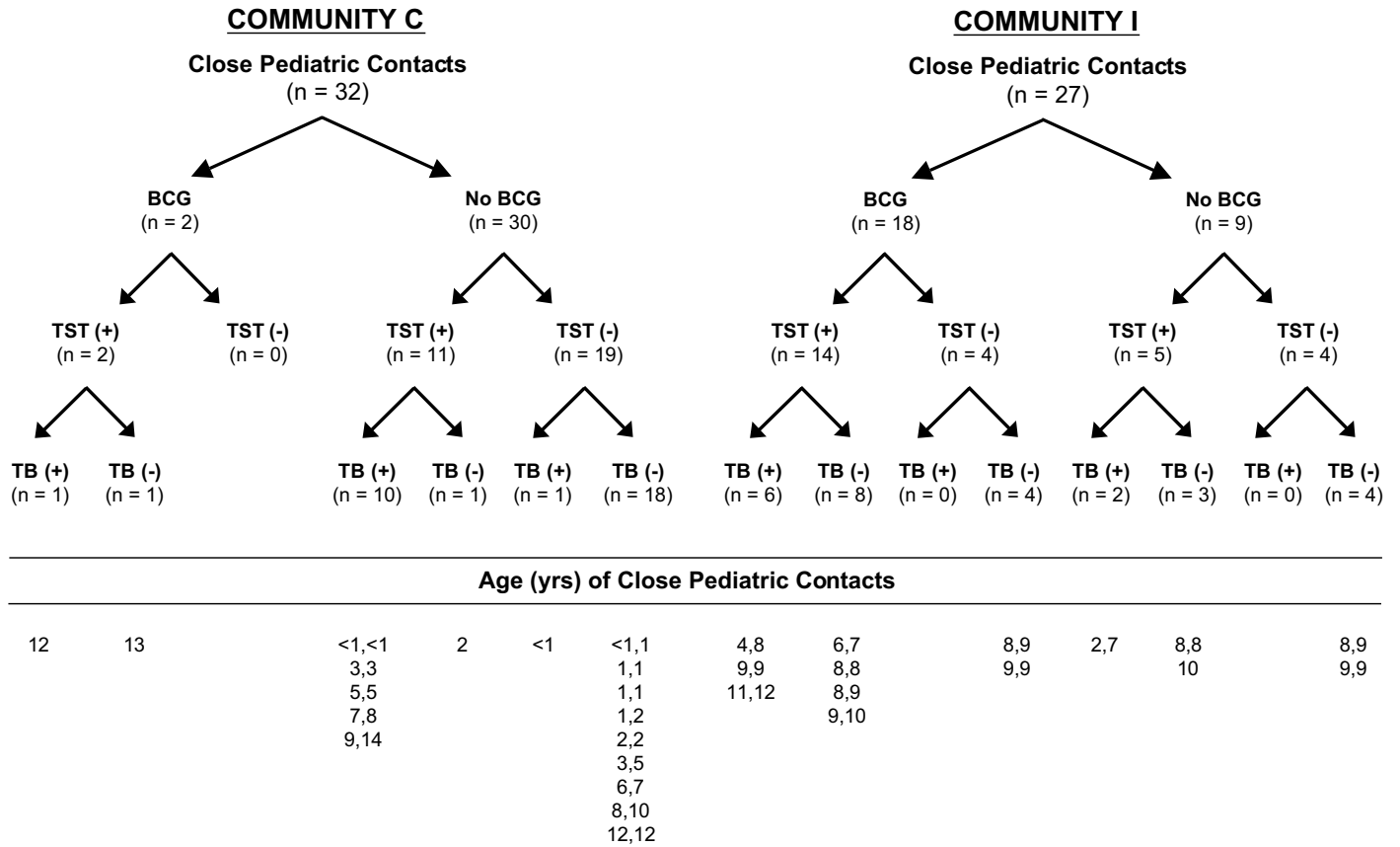


Figure 2. Outcome among close pediatric contacts in communities C And I
 The outcome of the screening of close pediatric contacts of the source cases in communities C and I is displayed, according to the BCG vaccination status, the tuberculin skin test (TST) status, and the tuberculosis disease status (TB) of the contact. The ages of the pediatric contacts are listed.

contacts in community I had been TST positive in the remote past. None developed TB disease. One of the close pediatric contacts in community C developed TB but did not convert their TST. BCG-vaccinated close contacts were more likely than BCG-unvaccinated close contacts to be newly infected (15/19 [78.9%] versus 13/36 [36.1%], p=0.003). Disease-to-infection ratios were higher in newly infected unvaccinated versus vaccinated close pediatric contacts (12/13 [92.3%] versus 7/15 [46.7%], p=0.02). More BCG unvaccinated than vaccinated newly tuberculin-positive close pediatric contacts were ≤ 5 years of age (8/13 [61.5%] versus 1 of 15 [6.7%], p=0.004). Independent of the TST, disease rates in the BCG vaccinated and unvaccinated close pediatric contacts were 7/20 (35.0%) and 13/39 (33.3%), respectively.

DISCUSSION

A protective effect of neonatal BCG vaccination in Canadian Prairie First Nations

was first demonstrated in a controlled trial in Saskatchewan in 1933-47¹³ and later confirmed in two case-control studies, one in Alberta in 1975-79,⁷ the other in Manitoba in 1979-83.¹⁴ Protection was greater in the earlier trial (80%) when the annual risk of infection or ARI was 7.6%, than in the later studies (60%) when the ARI was unknown, but on the basis of infection rates in neighbouring provinces, almost certainly much lower.^{15,16} Since these studies, it has become increasingly evident that neonatal BCG vaccination, although possibly reducing individual childhood morbidity, is a poor public health measure.^{17,18} It does not prevent infection¹⁹ and there is no good evidence that it protects against disease for more than 10 years after vaccination.²⁰ Accordingly, neonatal vaccination has little or no impact on the occurrence of tuberculosis in adults, who represent the largest pool of potential source cases. To reduce the ARI requires early case finding, case holding and completion of treatment.²¹

During the period 1991-2000, 41.5% and 19.5%, respectively, of the First Nation Community Health Centres in Alberta, reported potential source cases and pediatric cases (Figure 1). One small outbreak and two micro-epidemics, traceable to 3 source cases, accounted for 82.9% of the pediatric cases. Reports of micro-epidemics in Canadian Prairie First Nations first appeared in the 1960s.²² Molecular epidemiologic^{23,24} and other data^{25,26} suggest that a pattern of low endemicity, punctuated by outbreaks, is common to western Canada and characteristic of tuberculosis in decline.²⁷ Micro-epidemics appear to reflect a convergence of the many factors known to determine tuberculosis infection and disease in children (Table II).
 Among close pediatric contacts of the micro-epidemic source cases, infection rates and disease-to-infection ratios were very high. Similarly, high infection rates and disease-to-infection ratios had been reported in 1987 in another micro-epidemic in a northern Alberta First Nation community.⁴⁶ In that community,

TABLE II

Factors That Determine Whether a Child Will Become Infected with *M. Tuberculosis*, and If Infected, Progress to Disease

The risk of infection is usually a function of:

- 1) The presence of a source case; usually an adult,²⁸ but sometimes an older child or adolescent.²⁹⁻³¹
- 2) The source case's ability to transmit. Transmission is greater from patients who are sputum smear and culture positive versus smear-negative and culture positive.³²⁻³⁵ Transmission may also be influenced by the ability of the source case to aerosolize sputum; e.g., the strength and frequency of cough; sputum rheology.³⁶
- 3) The degree of contact the child has with the source case. Risk increases if the contact is close, indoors and prolonged.³²⁻³⁵

The risk of disease is usually a function of:

- 1) whether the infection is recent³⁷
- 2) age at infection³⁸
- 3) prior infection³⁹⁻⁴²
- 4) BCG status²
- 5) weight-for-height status^{43,44}
- 6) co-existent immunocompromising illness⁸
- 7) possibly genetic factors⁴⁵

tuberculosis had previously been very rare and no children had been BCG vaccinated. The source case in that micro-epidemic and in the two micro-epidemics reported here were otherwise well young adults with rapidly progressive (duration of cough 4 months, 6 weeks, and 4 months, respectively) highly infectious cavitary pulmonary tuberculosis. Two were young postpartum women. Age,³⁸ weight-for-height,^{43,44} and a genetic susceptibility⁴⁵ may have contributed to the high disease-to-infection ratios. However, disease-to-infection ratios of similar magnitude were reported in non-First Nations children in the pre-antibiotic and early antibiotic era.^{29,47-49} Historical differences in the time of first exposure to European settlers⁵⁰ and access to health care,⁵¹ may explain the propensity for the micro-epidemics to occur in the north.⁵²

In the present report, infection rates were almost certainly falsely high and as a result, disease-to-infection ratios falsely low, in BCG-vaccinated close pediatric contacts of the micro-epidemic source cases. The infection rate is determined by the TST. A BCG-related positive TST may occur for up to 2 to 3 years after neonatal BCG vaccination.⁵³⁻⁵⁵ Thereafter the BCG-related response has usually waned and a positive TST is interpreted to mean the child is infected with *M. tuberculosis*. However, this is not an infallible rule; a waned neonatal BCG-related tuberculin response may boost after repeated tuberculin testing.⁵⁶⁻⁵⁹ When interpreting the TST in the setting of contact tracing, the BCG history is ignored.¹⁰ Because some newly tuberculin-positive, previously

BCG-vaccinated close contacts were younger than 2 or 3 years of age and some of those older than 2 or 3 years of age were repeatedly tested, the true infection rate and disease-to-infection ratio in the BCG vaccinated are unknown. More newly infected BCG-unvaccinated than vaccinated children were ≤ 5 years of age, and therefore at higher risk of disease.³⁷

The converse of a falsely positive TST – i.e., a falsely negative TST – occurred in three of the micro-epidemic related pediatric cases. When the TST was ignored altogether, disease rates were virtually identical in BCG-vaccinated and unvaccinated close pediatric contacts.

Within the micro-epidemics, the evidence that BCG reduced the severity of disease was meager. CNS or disseminated disease occurred in 0 of 11 BCG-vaccinated and 1 of 20 BCG-unvaccinated pediatric cases. Other recent reports of BCG's protection are conflicting.^{60,61} Being retrospective, those reports and our own do not control for nutritional status, which may influence the protection offered by BCG.^{62,63} All cases of pediatric tuberculosis in the present report and all of those diagnosed in the 1987 micro-epidemic, completed a satisfactory course of treatment and there were no late sequelae. In the pre-antibiotic era, more than 50% of Aboriginal children with primary pulmonary tuberculosis developed complications and 10% died.⁶⁴ Between 1991 and 2000, one death due to disseminated BCG occurred in an interferon-gamma receptor deficient Alberta First Nation child.⁵

The promotion of BCG in most Alberta First Nations communities would appear

to be paradoxical.²⁸ Whereas outbreaks, which accounted for 82.9% of the pediatric cases, usually occur when the rate of infection is very low and a large percentage of the individuals exposed to tuberculosis are susceptible, advocates of BCG believe that vaccination is most useful when the rate of infection is high. An exceptional community may have a continuous high rate of tuberculosis without the occurrence of outbreaks. Presumably a large proportion of the population in these communities is already infected, making it difficult to recognize a sudden increase in the number of tuberculin reactors. In such communities, the use of BCG may be salutary and in accordance with international guidelines.⁶ At the time when micro-epidemics were more common in the general population, an expanded program of BCG vaccination was considered, but never adopted, as a means of protecting the susceptible.^{22,28,46} Broader BCG coverage of most First Nations communities is unlikely to be defensible on the basis of the ARI (measurable in unvaccinated children)^{6,65,66} or the meager benefit within the outbreaks described here. Serial tuberculin testing of pre-schoolers represents an alternative to BCG.

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RÉSUMÉ

Contexte : On réévalue actuellement au Canada la stratégie de contrôle de la tuberculose qui consiste à vacciner les nouveau-nés des Premières nations par le BCG (bacille Calmette-Guérin). Un examen de la morbidité récente due à la tuberculose infantile pourrait étayer cette réévaluation.

Méthode : Nous avons relevé les cas sources potentiels et les cas de tuberculose infantile chez les Premières nations de l'Alberta pendant la décennie 1991-2000, puis décrit la répartition de la maladie infantile. Nous avons ensuite déterminé l'effet du BCG sur la morbidité due à la tuberculose lors de deux grandes poussées épidémiques.

Résultats : En tout, 57 cas sources potentiels ont été déclarés dans 17 des 41 centres de santé communautaire des Premières nations dans les réserves (41,5 %), et 41 cas de tuberculose infantile ont été déclarés dans 8 des 41 centres (19,5 %). Trois poussées épidémiques dont a pu retracer les trois cas sources ont été à l'origine de 34 (18, 3 et 13, respectivement) des 41 cas de tuberculose infantile (82,9 %). Chaque poussée était distincte des autres dans l'espace et dans le temps. Chaque souche épidémique de *Mycobacterium tuberculosis* avait sa propre empreinte génétique. Lors des plus grosses poussées, les rapports maladie/infection (les taux d'attaque secondaire) étaient plus élevés chez les enfants non vaccinés nouvellement infectés en contact étroit avec des personnes atteintes que chez les enfants vaccinés (12/13 [92,3 %] contre 7/15 [46,7 %], $p=0,02$), mais le taux d'infection était presque certainement faussement élevé chez les enfants vaccinés par le BCG. L'un des enfants non vaccinés présentait un tuberculome des méninges en plus d'une tuberculose pulmonaire primaire.

Conclusion : Dans la plupart des communautés des Premières nations de l'Alberta, la répartition de la maladie dans le temps et dans l'espace et le maigre effet du BCG sur la morbidité mettent en doute le bien-fondé de continuer à administrer le vaccin.

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Book Review

Public Health and Preventive Medicine in Canada, 5th Edition

Chandrakant P. Shah. Toronto, ON: Elsevier Saunders, 2003; \$54.95

The 5th edition of this popular text on public health in Canada builds on its predecessors, expanding on the already broad range of topics addressed in previous editions. It incorporates the latest information on population health status and federal/provincial/territorial reports related to health care reform. Dr. Shah summarizes and links information from numerous data sources. Reviewers of this edition represent a broad cross section of the Canadian public health intelligentsia.

The intended readers of this text include health professionals, health administrators, policy makers, students at all levels, and the general public. It will be most appreciated by those interested in learning about the Canadian health system and its history, whether they come from a research or lay perspective.

In 600 pages, Dr. Shah covers a diverse range of health topics. The text is organized into three parts: Health and Disease,

The Health of Canadians, and The Health Care System. Appendix A provides summary tables of the preventive manoeuvres recommended by the Canadian Task Force on Preventive Health Care. Appendix B provides a set of educational objectives. There is a detailed Table of Contents and a well organized index. Both assist the reader in accessing needed information rapidly. Most chapters from previous editions have been substantially rewritten and updated.

Chapter 3 presents a conceptual framework of health indicators developed by Statistics Canada and the Canadian Institute for Health Information, and provides the definitions for many key health indicators. This chapter offers a nice link between Part I, which covers the key concepts and methodologies of public health and preventive medicine, and Part II, which could be seen as an application of these concepts and methodologies.

Part III provides an excellent overview of the origin, governing legislation and financing of the Canadian healthcare system. A new chapter on Quebec's health care system was written by Jean-Frederic Levesque and Pierre Bergeron. The final

chapter summarizes and compares key points from national documents, including those of Kirby and Romanow.

"Public Health and Preventive Medicine" is thoroughly researched, well organized, and very current. The breadth and depth of the information may prevent the book from being accessed by the general Canadian population, however they are necessary in order to maintain comprehensiveness and are reflective of the diversity of public health practice in Canada. Dr. Shah's text will continue to be used as an important resource by the next generation of Canadians working or interested in the public health system.

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