A fresh look at an old vaccine: Does BCG have a role in 21st century Canada?

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ABSTRACT

Introduction. In Canada, bacille Calmette-Guerin (BCG) vaccine is now primarily given to First Nations and Inuit (FNI) neonates living in tuberculosis (TB) endemic areas. With declining TB rates, attention has shifted from the protective effects of BCG to reports of serious vaccine-associated adverse events (VAAE). Methods. Surveillance data were reviewed to assess TB burden and trends, BCG coverage, and VAAE among FNI people in the 1990s. Results. TB among FNI people living on reserve was 25 times higher than the Canadian-born, non-Aboriginal rate between 1997 and 2000. Paediatric TB rates declined from 149 per 100,000 in 1990 to 23 per 100,000 in 2000, with one case of TB meningitis and one TB fatality (due to congenital TB) reported in the 0-4 age group. Nine cases of disseminated BCG infection occurred in a 21-year period among children with congenital or acquired immunodeficiencies. The estimated rate of disseminated BCG infection was 205 per 1,000,000 (95% CI 63 - 678). Discussion. BCG provides protection against severe forms of childhood TB. However, in a country with publicly funded health care and declining TB rates, it is important to consider VAAE. Disseminated BCG infection increases mortality among children with immunodeficiency disorders, which now have successful therapies. Although TB remains a threat in FNI communities, early detection and treatment of TB infection may be a more appropriate intervention.

Key Words: Aboriginal, Bacille Calmette-Guerin (BCG), Disseminated BCG disease, Tuberculosis, Vaccine Adverse Events, Canada

INTRODUCTION

Bacille Calmette-Guerin (BCG) is one of the oldest vaccines currently available. Mycobacterium bovis, though isolated in 1902, was attenuated via 231 serial passages for 13 years before it could be used as a vaccine in 1921 (1). The vaccine use in Canada dates to 1925, though its widespread use in publicly funded programs dates to 1948; this is the same year as the First International BCG Congress which led to the worldwide acceptance and use of the vaccine (2,3). The current vaccine strains used throughout the world derive from the parent strain created by Calmette and Guerin; however, due to continued serial passages, the strains worldwide have continued to differentiate until they were stabilised in the 1960s by lyophilisation and storage at low temperatures. The vaccine strains differ not only in their genetic composition, biochemical parameters, growth characteristics, colony morphology, but also in their ability to produce tuberculin reactivity or protection from tuberculosis (TB) (1, 4-5).

While the search for a safer and more effective TB vaccine is underway, we continue to use BCG, an 80-year-old vaccine. In Canada, BCG vaccine (Connaught, 1948) is primarily offered to First Nations infants living on reserves, and infants living in Inuit communities (5,6). Though there are a number of studies on vaccine efficacy which show conflicting results, studies in the Canadian Aboriginal population have shown significant protection (3,6-8). The earliest trial of BCG vaccine in
Saskatchewan in the 1930s and 40s showed the vaccine reduced the risk of TB death in infants by 80% (8). Two case control studies conducted in Manitoba and Alberta in the late 70s and early 80s have also demonstrated a 50-60% protection from TB disease in the vaccinated groups (3,6).

TB rates in Canada have decreased dramatically since the 1930s, and have continued to decline since the aforementioned case control studies were conducted. We wish to discuss whether it may be time to redefine the role of BCG vaccine in the Canadian context.

The objective of this paper is to examine the role of the BCG vaccine in the context of three parameters: the epidemiology of TB disease among First Nations people living on reserves in Canada; acceptability of the BCG vaccine; and BCG vaccine associated adverse events (VAAE).

METHODS

The epidemiology of TB (1990-2000)
The number of TB cases by age and sex for the First Nations, on-reserve population were provided by the First Nations and Inuit Health Branch (FNIHB) Regional TB programmes. TB case counts for other populations in Canada were obtained from publications of the Population and Public Health Branch (PPHB) of Health Canada. (9). Age-specific case fatality rates (CFR) etc. were calculated with a client-level data file provided by PPHB with all reported TB cases in the First Nations population living on and off reserve between 1990 and 2000. Analysis was done in SPSS® 11.0 (SPSS Inc., Chicago, IL). The TB rates were standardised to the 1996 Canadian population. Population estimates from the Indian Registered Population (IRP) were supplied by the Department of Indian and Northern Affairs (INAC). Rate calculations were carried out in Microsoft Excel. (Microsoft, Inc., Redmond, WA)

The number of TB cases by community have been available from the Regional TB programmes since 1997. We identified the communities with the ten highest cases between 1997 and 2000, and calculated incidence densities using population data from the IRP. Data from the FNIHB Community Workload Increase System (CWIS) were used to estimate the population of two of the communities, and to categorise the degree of isolation for all communities. Isolation types include remote isolated (no scheduled flights, no road access, and minimal telephone and radio); isolated (flights, good telephone service, no road access); semi-isolated (road access greater than 90 km from nearest physician services); and non isolated (road access less than 90 km from nearest physician services). CWIS is a database used to estimate health service and programme needs in First Nations communities. Estimations of housing densities, expressed as average persons per room (ppr), from the 1996 census were provided by INAC.

BCG coverage and adverse events
BCG vaccine coverage data were obtained from the FNIHB regional TB programmes. Data were available for the 1996-2000 period from British Columbia, Alberta, Saskatchewan, Manitoba, and northwestern Ontario. BCG vaccine adverse events have been located through literature search, and Health Canada’s VAAE database. This passive reporting system has maintained BCG VAAE information since 1987. A systematic review of this database was conducted in 2002 by Health Canada for BCG VAAE reported from 1993 to 2002.

The rate of disseminated BCG disease was calculated using the number of disseminated BCG disease cases reported in the above areas during the 1996-2000 period, and the estimated total number of doses given in the same area and time period.

RESULTS

The epidemiology of TB (1990-2000)
Figure 1 shows that standardised rates in the First Nations, on-reserve population have been consistently higher than overall Canadian rates. In 2000, the number of on-reserve cases was the lowest
ever reported, at 86 cases. The 1999 rate was ten times higher than the overall Canadian rate, while the 2000 rate (34 per 100,000) was six times higher. At the beginning of the decade, rates were highest among children aged 0-14 years, and adults aged 55 years or more (Figure 2). While rates in the paediatric population dropped throughout the 1990s, rates in other age groups appeared to be constant.

Between 1990 and 2000, 2,706 TB cases occurred in the First Nations population living on and off reserve. This represents 12.7% of the total reported cases in Canada during this eleven-year period. In 2000, 1.8% of the total Canadian population were First Nations people living on and off reserve. There were 1,418 cases (52.4%) among males. Ten percent of the cases were reported as relapsed TB, identical to the figure for the overall Canadian population during the same period. The rate of smear positive pulmonary TB was calculated for the four Western provinces (years 1998-2000) at 19.2/100,000.

A total of 855 (31.6%) cases were reported among children aged 0-14 years. Of these paediatric cases, there were eleven infections that resulted in severe TB disease (6 cases of miliary TB, and 5 of Central Nervous System (CNS) TB). The Rate of CNS TB in children 0-4 is 0.3/100,000 while among children aged 0-14 years it is 0.45/100,000. Rate
of miliary TB for children 0-4 years is 1.81/100,000, and for children 0-14 years it is 0.56/100,000. Reported case fatality was extremely low among children: out of 803 TB cases aged less than 15 years, one TB fatality (due to congenital TB) was reported; this amounts to a CFR of 0.12%.

While the overall rate of TB is decreasing on reserve, there is a shift towards microepidemics. Data on the ten communities with the highest reported TB cases during the 1997-2000 period are summarised in Table I. All of these communities had TB incidence densities higher than 100 per 100,000, and average housing densities in excess of 0.8 persons per room (ppr). The average housing density in Canada is 0.4 ppr. Only one of the communities was not considered isolated from physician services.

The overall rate in these ten communities was 395 per 100,000 (95% CI 344 - 455). Removing these communities from the First Nations calculations resulted in a First Nations, on-reserve rate of 27 per 100,000. This rate is still higher than the rate among foreign-born persons, Canadian-born, non-Aboriginal persons rate, and the overall Canadian rate. (Table III)

**BCG vaccine acceptance**

BCG vaccination programme is currently offered to on-reserve children in five of the ten provinces. Four of the remaining provinces discontinued their BCG programmes in the 1970s while one discontinued its programme in 2003. Provider and consumer acceptance of BCG vaccine varies between communities and is dependent on local experience with TB and BCG associated adverse events (VAAE).

Reported BCG coverage rates are shown in Table IV. An estimated 14,622 doses were administered in these areas during the 1996-2000 period. Vaccine coverage varies between communities within provinces, and also varies among provinces. In general, BCG vaccine coverage has declined in the late 1990s with uptake as low as 35% in British Columbia and as high as 98.5% in the Sioux Lookout Zone.

**BCG vaccine adverse events**

The true rate of local adverse reactions to BCG (e.g. localised abscess, suppurative adenitis) is difficult to estimate due to under-reporting. In

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**Table II. Characteristics of ten First Nations communities with the highest number of reported TB cases, and of Canada overall (1997-2000)**

| Community | Cases (Number) | Rate (per 100,000) | Average ppr | Isolation type |
|-----------|----------------|--------------------|-------------|---------------|
| 1         | 32             | 3670               | 0.8         | semi-isolated |
| 2         | 27             | 542                | 0.9         | isolated      |
| 3         | 27             | 315*               | 1           | isolated      |
| 4         | 26             | 939                | 1.1         | isolated      |
| 5         | 26             | 765                | 1.3         | isolated      |
| 6         | 16             | 494*               | 1           | isolated      |
| 7         | 12             | 330                | 1.1         | isolated      |
| 8         | 10             | 118                | 1           | non-isolated  |
| 9         | 10             | 117                | 1           | isolated      |
| 10        | 9              | 186                | 1.1         | remote        |
| Canada    | 7269           | 6                  | 0.4         | n/a           |

* Population data derived from Community Workload Increase System

**Table III. TB Rates in Canada by population subgroups (1997-2000).**

| Population                                           | TB Rate/100,000 people |
|------------------------------------------------------|------------------------|
| Ten First Nations Communities with the highest TB burden (table II) | 395                    |
| Remainder of First Nations communities               | 27                     |
| Total Canadian population                            | 6                      |
| Canadian-born Non Aboriginals                         | 1                      |

**Table IV. BCG coverage among on-reserve First Nation infants < 1 year old, 1996-2000**

| Regions                  | Coverage % | 1996 | 1997 | 1998 | 1999 | 2000 |
|--------------------------|------------|------|------|------|------|------|
| British Columbia         | 57.7       | 50.1 | 40.2 | 32.9 | 35.0 |      |
| Alberta                  | 60.3       | 54.1 | 56.3 | 55.3 | 50.8 |      |
| Saskatchewan             | 50.0       | 46.5 | 46.0 | 45.0 | 38.2 |      |
| Manitoba                 | 89.0       | 78.5 | n/a  | n/a  | 85.4 |      |
| Sioux Lookout Zone       | 98.5       | 95.0 | 85.0 | 45.0 | 78.8 |      |
British Columbia, for the years 1987-1992, a 0.24% VAAE rate was reported for approximately 3000 vaccinations. This rate dropped to 0.01% following reduction in dose to 0.025 mL (10).

Systemic adverse reactions to the vaccine include osteomyelitis and disseminated BCG disease. For the period 1993 to 2002, two cases of osteomyelitis and six cases of disseminated BCG disease were identified in Canada following a systematic review of the adverse event reporting system. An additional three disseminated BCG disease cases were reported outside this period, two in the eighties and one in 2003 (Table V).

Eight of the nine cases of disseminated BCG disease were in First Nation and Inuit children. The non First Nation and Inuit child received the BCG vaccine at birth in their country of origin and developed disseminated disease 6.5 years later. All of the children had a genetic or acquired immune deficiency. Of the two cases documented in the literature, the first case was in a British Columbia infant with an undiagnosed immune defect in 1982, and the second in a Quebec infant with HIV in the mid 1980s (10,11). Of the six cases reported to the VAAE database, one infant had HIV, four infants had Severe Combined Immune Deficiency (SCID), and the last had interferon gamma receptor deficiency. The last Canadian case reported in 2003 was in a child with SCID. There were eight fatalities in these nine cases; however not all were directly related to disseminated BCG disease. The remaining children died of multiple infections (including BCG), and one child died of complications from bone marrow transplant. In all cases, BCG vaccine contributed to severe disease.

### Table V. Cases of Disseminated BCG disease in Canada. VAAE = Vaccine associated adverse events.

| Case Number | Source of Case Information | Year of diagnosis | Case details | Underlying Immunodeficiency |
|-------------|---------------------------|------------------|--------------|-----------------------------|
| 1           | Fitzgerald, 2000          | 1982             | FNI child vaccinated in BC, cause of death not documented | Undiagnosed congenital immunodeficiency |
| 2           | Houde, 1988               | mid 1980's       | FNI child vaccinated at birth, complicated course, multiple infections including disseminated BCG disease, died of PCP pneumonia | HIV |
| 3           | Health Canada’s VAAE data base | 1993          | FNI child vaccinated at 3 days of age in Manitoba, child died of disseminated BCG disease | SCID |
| 4           | Health Canada’s VAAE data base | 1996          | FNI child vaccinated at 3 weeks of age in Alberta, child died of multiple infections | Interferon gamma receptor deficiency |
| 5           | Health Canada’s VAAE data base | 1996          | FNI child vaccinated at 3 days of age in Manitoba, died of multiple infections | HIV |
| 6           | Health Canada’s VAAE data base | 1997          | FNI child vaccinated at 1 day of age in Manitoba, died of multiple infections | SCID |
| 7           | Health Canada’s VAAE data base | 1998          | FNI child vaccinated at birth in NWT, died post bone marrow transplant | SCID |
| 8           | Health Canada’s VAAE data base | 1999          | Child vaccinated at birth in Iran, developed disease 6.5 years later, survived | SCID |
| 9           | Health Canada’s VAAE data base | 2003          | FNI Child vaccinated at birth in Manitoba; died of multiple infections | SCID |
Three of the above cases of disseminated BCG disease occurred in the areas and during the time period summarized in Table III. The estimated rate of disseminated BCG disease was 205 per 1,000,000 doses (95% CI, 62, 678).

DISCUSSION

Various benchmarks of TB incidence have been proposed as indicators of the burden of TB disease in populations (12,13). According to these, populations in which TB incidence is 100 per 100,000 or higher can be said to be at "high risk" for TB, while rates of less than 10 per 100,000 indicate a "low risk" for TB. Applied to the data in this report, the First Nations population has not reached a level of low risk, though the overall TB incidence rates are declining. Many First Nations communities are certainly at high risk for disease with a shift to microepidemics. Rates of paediatric disease have declined quite rapidly in the last ten years, with very few cases of severe paediatric TB disease noted, and one fatality. TB continues to be particularly problematic in rural and remote communities where overcrowding plays a role in disease transmission, chronic illnesses contribute to reactivation of old disease, and early diagnosis is challenging due to nursing shortages experienced by these Canadian communities.

BCG vaccine has been used to protect First Nations children from severe TB (CNS and miliary) disease. Our data show that for a recent eleven-year period, eleven cases of severe TB disease were noted in FNI children; none of these were fatal. The one TB fatality was due to congenital infection. While the numbers are small, the rates are greater than that advised by IUATLD as criteria for discontinuation of BCG vaccine (14). The decreasing rate of paediatric TB disease in Canada is occurring concomitantly with decreasing vaccine acceptance and coverage, and hopefully improved access to medical care. The calculated rate of disseminated BCG disease is manyfold higher than previous estimates in Canada (20/1,000,000 doses); this rate was based on a denominator of vaccine doses distributed by the pharmaceutical company rather than the number of doses actually delivered (15). The underestimation in rate is understandable, given that BCG is delivered in a multidose vial (ten doses per vial) and usually only one dose per vial is utilised. Our rate is also higher than noted in the literature: 0.19-1.56/1,000,000 doses (1,16).

There are no population-based studies to date to document the rate of congenital immune deficiencies in Canadian First Nations children. There is evidence to indicate that other indigenous populations may experience a higher rate of immunodeficiencies (17). Disseminated BCG disease in the context of HIV infection is theoretically preventable by conducting prenatal screening, though there is always the concern of missing infection in the window period. Currently there are no antenatal screenings available for genetic immunodeficiencies. Children with SCID, if not given BCG at birth, have a good prognosis with bone marrow transplant within the first few years of life (18).

 Cure rates are 90% for recipients of HLA-identical transplants, 75% for recipients of matched, unrelated transplants, and 67% for North American Athapascan Aboriginal people (18-20).

Principles of TB control are simple: early case finding, contact tracing, and treatment of latent infection; however, such a programme requires an infusion of resources and commitment by all levels of government. Given our local experience with severe adverse events associated with BCG vaccine, BCG vaccine use in Canada is currently being reviewed.

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