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Benefits and Risks of Neonatal Bacille Calmette-Guérin (BCG) Vaccination among Aboriginal Infants in Canada: Assessment by Markov Model

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Benefits and risks of neonatal bacille Calmette-Guérin (BCG) vaccination among Aboriginal infants in Canada: assessment by Markov model

by

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Thesis submitted to

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in partial fulfilment of the requirements for the

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University of Ottawa

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ABSTRACT

Bacille Calmette-Guerin (BCG) vaccine is given to Canadian Aboriginal neonates in communities at high risk for tuberculosis (TB). However, severe reactions and deaths associated with the vaccine have been reported among infants born with immunodeficiency syndromes. A Markov model was developed to estimate the burden of TB among Canadian Aboriginal children, evaluate the effectiveness of BCG vaccination, and estimate threshold values for severe combined immunodeficiency (SCID) incidence at which a BCG program will reduce quality-adjusted life expectancy. Estimated thresholds for SCID are lower than the rate reported in one North American Aboriginal population, regardless of the assumed risk of tuberculous infection. The possibility that Canadian Aboriginal children are at increased risk for SCID has serious implications for continued BCG use in this population. In this context, enhanced TB Control – including early detection and treatment of infection - may be a safer, more effective alternative.
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# TABLE OF CONTENTS

ABSTRACT .................................................................................................................. i

ACKNOWLEDGEMENTS ............................................................................................ ii

TABLE OF CONTENTS ............................................................................................. iii

LIST OF TABLES .......................................................................................................... v

LIST OF FIGURES ...................................................................................................... vi

1 INTRODUCTION ..................................................................................................... 1
  1.1 Transmission and pathogenesis of tuberculosis ............................................... 1
  1.1.1 Tuberculous infection and disease ............................................................... 1
  1.1.2 Tuberculosis in children ............................................................................. 2
  1.2 Epidemiology of tuberculosis .......................................................................... 3
  1.2.1 Global burden of disease ........................................................................... 3
  1.2.2 Tuberculosis among Aboriginal peoples in Canada ................................... 4
  1.3 Bacille Calmette-Guérin (BCG) vaccine .......................................................... 6
  1.3.1 Evidence for the effectiveness of BCG ....................................................... 6
  1.3.2 Adverse reactions associated with BCG ..................................................... 9
  1.3.3 Immunodeficiency disorders and the risk of disseminated BCG infection .... 11
  1.3.4 BCG use in Canada .................................................................................... 13
  1.3.5 Adverse reactions in the Canadian Aboriginal population ...................... 14
  1.4 Decision analysis ........................................................................................... 17

2 OBJECTIVES .......................................................................................................... 19

3 METHODS ............................................................................................................. 20
  3.1 Structure of decision model .......................................................................... 20
  3.1.1 Intervention ............................................................................................. 20
  3.1.2 Markov health states ............................................................................... 21
  3.2 Assumptions .................................................................................................. 23
  3.3 Input data ...................................................................................................... 25
  3.4 Outcomes ...................................................................................................... 28
  3.5 Variability and uncertainty analyses ............................................................... 29

4 RESULTS .............................................................................................................. 31
  4.1 Probability estimates ..................................................................................... 31
  4.2 Utility values for tuberculosis states .............................................................. 35
  4.3 Base case analysis ......................................................................................... 38
  4.4 Markov cohort analyses ................................................................................ 38
  4.5 Estimations of the burden of disease and deaths caused by TB .................... 41
LIST OF TABLES

Table 1. BCG coverage (%) among First Nations infants aged less than one year, by region (1996-2000) .................................................................14

Table 2. Summary of disseminated BCG infection cases among Canadian Aboriginal infants (1983 – 2003) .............................................................................16

Table 3. Input data for Markov model ..........................................................34

Table 4. Number of total TB cases and case fatality rate among First Nations people in Canada, by age and disease site (1990-2000) .................................................................35


Table 6. Mean utility scores for neurological sequelae following acute meningeval TB, by group, sex, level of education, parental status, and age group .................................................................37

Table 7. Estimated life expectancy, QALYs, and discounted QALYs, by ARI and BCG program decision (birth to age 14 years) .................................................................38

Table 8. Estimated TB case tallies and deaths in a birth cohort of 100,000, by ARI and BCG program decision (birth to age 14 years) .................................................................41

Table 9. Effects of varying parameter estimates on the threshold SCID incidence at birth in a population with an ARI of 0.1% .................................................................48

Table 10. Results of Monte Carlo simulations, assuming different risks of SCID in neonates ..................................................................................51

Table 11. Threshold values of SCID incidence estimated from Monte-Carlo simulations ..................................................................................52
LIST OF FIGURES

Figure 1. Decision model for BCG vaccination at birth to age six months..................21

Figure 2. Markov health states after the first cycle in the model..............................22

Figure 3. Markov cohort analysis with an ARI of 1%, in the absence of BCG vaccine and SCID.............................................................39

Figure 4. Markov cohort analysis with an ARI of 0.1%, in the absence of BCG vaccine and SCID .............................................................40

Figure 5. Estimated TB rate (all forms), by BCG program decision and ARI (%)........43

Figure 6. Estimated meningeal TB rate, by BCG program decision and ARI (%)..........44

Figure 7. Estimated miliary TB rate, by BCG program decision and ARI (%)............45

Figure 8. Estimated cumulative incidence of neurological sequelae, by BCG program decision and ARI (%)..............................................46

Figure 9. Two-way sensitivity analysis on the assumed ARI (%) and the incidence of SCID at birth in the population.................................................49

Figure 10. Three-way sensitivity analysis on the risks of primary TB, BCG infection among vaccinated infants with SCID, and SCID at birth (ARI = 0.1%).................50
1 INTRODUCTION

1.1 Transmission and pathogenesis of tuberculosis

1.1.1 Tuberculous infection and disease

Tuberculosis (TB) is caused by the bacteria *Mycobacterium tuberculosis*. It is generally accepted that infection with the organism is lifelong (1), and that disease may occur soon after primary infection (the period of highest risk) or many years later through endogenous reactivation. Primary infection is usually self-limited, characterized by subpleural lesions and enlarged lymph nodes (the Ghon complex) which undergo fibrosis and calcification (2). Disease will develop in a minority of immunocompetent individuals who are unable to limit the replication of bacilli. Asymptomatic dissemination may also occur, seeding pulmonary and extrapulmonary sites such as the lung apices and kidney, respectively (3).

It is often stated that an individual infected with *M. tuberculosis* has a 5% risk of disease within two years of exposure, and an overall 10% lifetime risk of disease (3,4). Although this is a useful generalization, recent modelling studies have estimated the risk of disease soon after primary infection may vary between 14% and 29% (5-8). All studies agree that the majority of people with latent infection will never develop disease. However, medical and social conditions such as HIV/AIDS (9), malnutrition (10), diabetes (11), and substance abuse (12), can elevate the risk of disease among those with longstanding latent infection.
Among those who do not progress to disease during primary infection, postprimary TB may develop after a variable period of latent infection. Postprimary TB can appear in almost any part of the human body. Pulmonary and laryngeal forms of disease are usually infectious to others, particularly if *M. tuberculosis* can be isolated from a sputum sample using smear microscopy (13). Although they are generally less infectious, smear-negative cases with a positive sputum culture result may also excrete bacilli (14). The organism is spread to the lungs of others through airborne droplets, which are excreted by infectious individuals when they cough, sneeze, laugh, or talk.

1.1.2 *Tuberculosis in children*

The risk of TB disease following infection is highly dependent on the age of children. In very young children (age 0-4 years) who are infected, the risk is as high as 30%, the highest of any age group (1, 15, 16). Conversely, the risk of disease among 5-14 year olds is likely the lowest of any age group (17). The distribution of disease by diagnostic site also differs with age: children aged 0-4 years are more likely to develop meningeal, disseminated (miliary), or lymph node TB; while older children present more with pleural disease (17-19). Miliary TB in children tends to appear among the very young, the median age at diagnosis being 10.5 months (20). If symptomatic lymphohematogenous spread does occur during primary infection in young children, it usually does so quite rapidly (3-6 months) after initial exposure to *M. tuberculosis* (16, 21). This leads to miliary TB and tuberculous meningitis, with high risks of death or disability.
The existence of pediatric TB in a community is an indicator of uncontrolled transmission, due to either outbreaks or poorly controlled, endemic TB. It is also associated with socio-economic conditions, and above all overcrowded living conditions, which increase the likelihood of transmission (22). In communities at high risk for TB, it is essential that infectious cases are found rapidly to shorten the exposure of children to airborne bacilli. It is also important to provide aggressive treatment of asymptomatic infection to exposed children, particularly those aged less than five years (23). Bacille Calmette-Guérin (BCG) vaccine may also be used in these settings, to prevent meningeal and miliary TB from occurring (24-27).

1.2 Epidemiology of tuberculosis

1.2.1 Global burden of disease

TB remains one of the top ten causes of death in the world (28). Of all infectious organisms causing disease, *M. tuberculosis* arguably causes the most deaths worldwide each year. According to the World Health Organization (WHO), an estimated 8 million TB cases and 1.9 million TB deaths occurred in 1997. The highest proportion of cases worldwide, and the highest incidence rates, were reported in Asia and sub-Saharan Africa (29). It has been estimated that 100,000 children aged 0-4 years (30), and 400,000 children under the age of 15 years, die each year from TB (31).

It is thought that one third of the world’s population is infected with *M. tuberculosis* (31). In many countries the reservoir of infection is mainly confined to older
age groups, who were exposed to infection many years ago. Perhaps the best indicator of
the TB situation in a population is the number of new tuberculous infections occurring
each year, referred to as the annual risk of infection (ARI) (4). This parameter is
important for two reasons: 1) the occurrence of new infections is a sign of ongoing
transmission that perpetuates TB in a population; and 2) the risk of disease is highest
during the first few years after initial infection (32). The ARI likely exceeds 1% in most
African and Asian countries, and its decline is heavily dependent on access to health care
and the availability of TB services. In most industrialized countries, the ARI is less than
0.1%, declining at a rate of more than 10% per year (31).

1.2.2 Tuberculosis among Aboriginal peoples in Canada

In the first half of the 20\textsuperscript{th} century, TB death rates in the First Nations and Inuit
(Aboriginal) populations of Canada were among the highest ever reported in a human
population. After the introduction of antitubercular chemotherapy in the 1940s and
1950s, death rates in the First Nations population plummeted from 700 per 100,000 to
less than 100 per 100,000 in approximately ten years (33). In 1950 the death rate among
Inuit Canadians was also approximately 700 per 100,000, decreasing markedly after the
implementation of aggressive interventions (34, 35). Despite these reductions in
mortality, generations of Aboriginal people were exposed to the tubercle bacillus during
this era (36), and thus developed longstanding latent infection. This fact, coupled with an
ongoing cycle of transmission in many communities, led to the high prevalence of latent
tuberculous infection (making the conventional assumption that infection is lifelong) among First Nations adults today (37).

TB rates among First Nations people in Canada remain ten times higher than overall Canadian rates, and 30 times higher than Canadian-born, non-Aboriginal rates (37-39). Rates are highest among First Nations people in the prairie provinces (Alberta, Saskatchewan, and Manitoba), and among the Inuit in northern Canada (40). In 2001, the rate among Inuit people was the highest of any ethnic population (82 per 100,000), while TB among non-Aboriginal people born in Canada is in the elimination phase, with an incidence of one per 100,000 persons (39). Social and medical risk factors such as substance abuse and HIV/AIDS, respectively, increase the risk of progression to disease among infected Aboriginal people (41), and overcrowded housing increases the risk of transmission to susceptible individuals (42). The combination of these factors in a community can lead to large TB outbreaks, in which one source case is responsible for infecting many contacts, and progression to disease after conversion of the tuberculin skin test is rapid (43). A recently published study suggests that infected Aboriginal individuals may be genetically predisposed to developing disease (44), similar to the increased susceptibility observed in a west African population (45).

High rates of pediatric TB have been reported among First Nations children, particularly in Saskatchewan (37). These high rates are a sign of uncontrolled transmission in many communities (46). In communities where TB has not occurred for long periods, large clusters of pediatric disease may suddenly occur due to delayed finding of an infectious source case (47). The disproportionate burden of childhood TB
among Aboriginal peoples has led to the development of school screening programs (48), and the continued use of BCG vaccine in many communities.

1.3 Bacille Calmette-Guérin (BCG) vaccine

Bacille Calmette-Guérin (BCG) is a live, attenuated vaccine derived from the organism Mycobacterium bovis. The vaccine provides partial protection against TB disease, particularly meningeal and miliary TB in children (24-27). Many different strains of BCG are currently in use around the world, all of which are descendents of the original culture used in 1921 (49). The vaccine is available in Canada as a lyophilized culture of live bacilli. The dose is generally 0.05 mL in neonates, given intradermally (50).

1.3.1 Evidence for the effectiveness of BCG

BCG is the most controversial of routinely administered vaccines, and its efficacy has been widely debated. To date more than 3 billion people have been vaccinated (51). Meta-analyses of results from clinical trials and case-control studies have shown an average protective effect against TB disease (all forms) of 50% (27). It is generally accepted that the vaccine provides protection against severe forms of paediatric TB, such as miliary disease and tuberculous meningitis. Case-control studies from South America have estimated that BCG reduces the risk of TB meningitis by 100% (24), and 80% (95%
CI 41, 93) (25). The results of two meta analyses indicate that risks of meningeal and miliary TB are lowered by 86% (95% CI 65, 95) (26), and 78% (95% CI 58, 88) (27).

Estimates of protection from studies published in the literature vary widely, from 0 to 80%. Widespread concerns were raised after the largest controlled field trial to date, in which more than 360,000 Indian children were vaccinated with the most common strains of BCG (Danish and Paris), showed no protective effect (52). A major limitation of the study was that children were not assessed for infection status at the time of vaccination (at age eleven years), and BCG would have no effect among children who were previously exposed to *M. tuberculosis*.

Randomized trials have also shown appreciable protection following BCG vaccination. Ferguson and Simes found that BCG reduced the risk of TB death by 80% among First Nations infants (less than one year of age) in Fort Qu’Appelle, Saskatchewan (53). Death rates observed in cohorts of vaccinated infants and controls in that study were 99.4 per 100,000, and 490 per 100,000, respectively. Greater protection was observed in children vaccinated at six months of age or older than among those vaccinated as neonates. In addition to the very different epidemiologic situation when compared to today, the study evaluated a different strain and different dosage of BCG. A protective effect of 75% was observed among vaccinated infants in Chicago (54), while the British Medical Research Council found a protective effect against all forms of TB of 78% among children vaccinated at age 14-16 years (55). In the latter study, annual rates of disease among vaccinated and unvaccinated subjects were 0.28 per 1,000 and 1.28 per 1,000, respectively. Ten cases of meningeal or miliary TB developed among unvaccinated subjects, while no cases were reported among children who received BCG.
Of note when considering the evidence above is that BCG seems to provide more protection in settings located farther from the equator (56). There are several theories as to why this has occurred. Populations living closer to the equator are exposed to higher levels of environmental mycobacteria early in life, which may provide some natural immunization and in doing so mask the effects of BCG (57). It has also been hypothesized that BCG protects against primary infection and endogenous reactivation disease, but has little impact on preventing disease due to exogenous reinfection (58). In high-incidence countries such as India children may be bombarded with several strains of TB early in life, and BCG may have no effect in settings where this repeated exposure is happening. Efficacy may also vary due to the many different strains of BCG used throughout the world (49), or differences in host susceptibility to TB between populations. The evolution of cultured *M. bovis* may play a significant role in this variance, and may have also resulted in an overall reduction in immunogenicity over time (59). All currently used vaccines are descended from the original cultures of Calmette and Guérin in 1921, derived from repeated subculturing since that time. Conversely, *M. tuberculosis* may have adapted over time to BCG-induced immunity, as it has been exposed to BCG for eight decades in which over 3 billion people have been vaccinated (60).

Colditz et al. (27) concluded that BCG may provide up to 10 years of protection following vaccination. Estimates of duration of protection from other studies vary. In Britain it was found that BCG still provided some protection 10-15 years later, although it had waned (55). Other studies have shown that efficacy is constant for many years after vaccination, but that efficacy was quite low. For example, Comstock et al. (61)
found that protection remained as low as negative 57% among Georgia children, and that no statistically significant effect was present among Puerto Rican children soon after and 20 years following vaccination (62).

Many vaccines are considered valuable for their herd immunity effects, as increasing coverage will lessen the proportion of susceptibles to a level at which transmission can no longer occur. Evidence that BCG has any such effect is lacking (63). There are several possible explanations for this: protection against pulmonary, infectious disease is unclear and widely debated; BCG is often given to neonates, and children are rarely infectious (17); BCG protection may wane before a child reaches adulthood (27) when the individual is more likely to progress to infectious TB; and finally, TB has persisted in human populations despite 3 billion doses given (64).

1.3.2 Adverse reactions associated with BCG

The development of a scar (3-7 mm) following vaccination is considered a normal reaction to BCG. Adverse local reactions include suppurative adenitis and localized abscess (50). A review of surveillance data from various European countries found that 0.039% of vaccinated infants aged less than one year experienced suppurative adenitis (65).

There are two forms of serious systemic adverse reactions to BCG: osteomyelitis and disseminated infection. Both are rare. The risk of osteomyelitis increases when BCG is given in the gluteal region or thigh, as observed in Scandinavian populations. The rate of osteomyelitis was more than 40 times higher in Finland and Sweden than in
other European countries, where rates were consistently lower than 2 per 1,000,000 vaccinated people (66).

The most severe and life-threatening adverse event associated with BCG is disseminated infection. Since BCG vaccine is a culture of live bacilli, it may cause serious infections in an immunocompromised host. Although idiopathic cases have been reported (67, 68), this complication generally appears among infants with an acquired or congenital immunodeficiency (69). A European study that reviewed data from several countries for a period of 27 years found that the overall rate of disseminated infection was 1.35 per 1,000,000 vaccinated persons, although there were considerable discrepancies between populations (66). A rate of 3.4 per 1,000,000 vaccinated newborns was reported in Chile (70). Case fatality rates of 83% and 80% have been reported in a case series review (71) and a review of European surveillance data (66), respectively. Talbot et al. (71) used the following case definition for disseminated infection: 1) BCG was cultured from a specimen; and 2) either a blood or bone marrow culture was positive or there was evidence of infection at two or more anatomic sites beyond the region of vaccination; and 3) a systemic syndrome compatible with mycobacterial disease was diagnosed. The disease may occur soon after infection, or following long latent periods (72).
1.3.3 Immunodeficiency disorders and the risk of disseminated BCG infection

Underlying conditions most frequently associated with disseminated BCG infection include severe combined immunodeficiency (SCID), HIV/AIDS, chronic granulomatous disease (CGD), and more recently disorders of IL-12 or interferon gamma-mediated immunity (69, 73). SCID refers to a series of autosomal recessive and x-linked recessive disorders, in which deficiencies of adenosine deaminase, T and B cells, and/or natural killer cells may be present (74). Studies from Sweden, Switzerland, and France have estimated SCID rates of approximately one per 100,000 newborns (75-77). Prior to 1968, fatality among infants with SCID was 100% (78). The availability of bone marrow transplantation has changed this situation dramatically. Data from the International Bone Marrow Transplant Registry has shown that 90% of infants survive if an HLA-identical donor is available (79). At Toronto Sick Kid’s Hospital, 75% of infants survived following transplants from matched, unrelated donors (80). O’Marcaigh et al. (81) found that 67% of infants from Athabaskan-speaking populations in North America survived SCID, including two out of three Canadian Dene infants. Successful treatment of disseminated BCG infection with anti-mycobacterial medications – followed by bone marrow transplantation – has been reported in children with SCID (82). However, nine out of ten cases are fatal (71).

Although the incidence of SCID among Canadian Aboriginal people is unknown, the disease has been reported among several ethnically and linguistically distinct populations. These include the Dene of northern Canada, an Inuit child, and First Nations children from Manitoba (81, 83). Incidence among the Navajo in the United
States between 1969 and 1982 was 52 per 100,000, far in excess of what is expected (84). It is possible that the risk of SCID among Aboriginal Canadian and American Indian newborns is higher than in other populations.

Interferon-gamma receptor deficiency was reported in a First Nations infant from Alberta, in 1997 (83). The infant was homozygous for a deletion on chromosome 6. Although the mother was heterozygous for the deletion, the investigators were unable to assess the father (85). This and other disorders known to affect components of the immune system needed to fight *M. tuberculosis* have been grouped together and termed Mendelian susceptibility to mycobacterial disease (MSMD) (73). It is certain that these disorders would not have been properly diagnosed in the absence of new technologies, and many cases of idiopathic disease in the past may have occurred among children with unknown immunodeficiencies. In a review by Casanova et al., five out of 16 idiopathic BCG infection cases were first cousins, and seven out of the 16 had other severe opportunistic infections (68), suggesting undetected immunodeficiencies may have been present.

It has been estimated that the probability an HIV-infected child will develop a disseminated BCG infection following vaccination is quite low, from 1-3% (86, 87). In fact, the WHO continues to recommend BCG in areas where HIV vertical transmission is frequent, as the risk of TB in children is far greater than the risk of BCG-associated disease (88). When disseminated BCG infection does occur in HIV-infected individuals, reported case fatality is 78% (71).
1.3.4 BCG use in Canada

BCG was first field tested in Canada among the First Nations children of Fort Qu'Appelle, Saskatchewan, in 1933 (53). Following the First International Congress on BCG in 1948, mass BCG vaccination programs were implemented in Quebec and Newfoundland (33). Although these were the only provinces to do so, programs to vaccinate high-risk groups were started in other selected areas (89). For example, the federal government policy of BCG vaccination on reserves began around this time.

Among First Nations infants in Canada, three studies have shown a protective effect following BCG vaccination. In addition to the work of Ferguson and Simes described above (53), two case-control studies have been done. The first showed a reduced risk of 61% (95% CI 31, 78) among First Nations children in Manitoba (90), while the second found that BCG reduced risk by 57% (95% 25, 77) in Alberta First Nations children (91). No field trial has been done to evaluate the current strain of BCG used in Canada.

Aboriginal newborns represent the only group in Canada to receive BCG as part of a routine vaccination program. The First Nations and Inuit Health Branch (FNIHB) of Health Canada has maintained this policy due to the higher risk of TB in First Nations communities, although it is not in effect in all areas. Currently, the decision to use BCG in a given community is the responsibility of the FNIHB Regional Director, based on recommendations of the community, the regional TB medical consultant, the regional Medical Officer of Health, and/or appropriate TB program staff (37). BCG coverage estimates in five populations between 1996 and 2000 are shown in Table 1.
Table 1. BCG coverage (%) among First Nations infants aged less than one year, by region (1996-2000)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific (British Columbia)</td>
<td>57.7</td>
<td>50.1</td>
<td>40.2</td>
<td>32.9</td>
<td>35.0</td>
</tr>
<tr>
<td>Alberta</td>
<td>60.3</td>
<td>54.1</td>
<td>56.3</td>
<td>55.3</td>
<td>50.8</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>50.0</td>
<td>46.5</td>
<td>46.0</td>
<td>45.0</td>
<td>38.2</td>
</tr>
<tr>
<td>Manitoba</td>
<td>89.0</td>
<td>78.5</td>
<td>n/a</td>
<td>n/a</td>
<td>85.4</td>
</tr>
<tr>
<td>Sioux Lookout (northwestern Ontario)</td>
<td>98.5</td>
<td>95.0</td>
<td>85.0</td>
<td>45.0</td>
<td>78.8</td>
</tr>
</tbody>
</table>

Source: coverage estimates reported by the FNIHB Regional TB Programs

1.3.5 Adverse reactions in the Canadian Aboriginal population

The overall rate of BCG-associated adverse reactions in Canada has been difficult to estimate due to under-reporting. A report on the experience in British Columbia from 1987 to 1992 showed that 0.24% of approximately 3000 vaccinated persons had an adverse reaction. When the dose in that province was reduced from 0.1 mL to 0.025 mL, the adverse event rate dropped to 0.01%. This report also referred to a fatal case of disseminated BCG infection during the 1980s (92).

Recently, a case of osteomyelitis was reported in an Inuit infant from Nunavut (personal communication with Dr. Ann Roberts, Medical Officer of Health, Nunavut).
The child was given one year of antitubercular medications, and survived. No immunodeficiency was detected, and all siblings in the family remain healthy.

Eight known cases of disseminated BCG infection in the Canadian Aboriginal population are summarized in Table 2. Most cases have been associated with congenital immunodeficiencies. Two HIV-infected First Nations infants have been diagnosed with disseminated BCG infection. Both infants died, although successful antitubercular therapy had been given in both cases - the first a child from Quebec (93), and the second a child from Manitoba (83) – before the fatality occurred. Another infant born to an HIV-positive mother was recently given BCG vaccine, when it was clearly contraindicated. These reports have led to a new FNIHB policy: BCG vaccine cannot be given to the infant or child unless the mother tests negative for HIV while she was pregnant and has not since had unprotected sex with a different partner or taken drugs by injections. If the mother cannot be tested, then the infant or child needs to be tested before receiving the vaccine.

Much like in developing countries now, the possibility of undetected adverse reactions to BCG before the 1980s should also be considered. In a review of autopsies at the Winnipeg Children’s Hospital published in 1982, it was found that 26 of 36 infants given BCG as neonates had tuberculoid granulomas in various sites. In twelve of the infants, lesions were confined to the site of vaccination, and ipsilateral axillary or cervical lymph nodes. The remaining 14 had granulomas in distant sites. However, the authors did not associate any significant disease with *M. bovis* in these infants (94).
Table 2. Summary of disseminated BCG infection cases among Canadian Aboriginal infants (1983 – 2003)*

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Year</th>
<th>Province/territory</th>
<th>Underlying immunodeficiency</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1983-7**</td>
<td>B.C.</td>
<td>Unknown</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1988</td>
<td>Quebec</td>
<td>HIV</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>1993</td>
<td>Manitoba</td>
<td>SCID</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>1996</td>
<td>Manitoba</td>
<td>HIV</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>1996</td>
<td>Alberta</td>
<td>IFN-γ receptor deficiency</td>
<td>83, 85</td>
</tr>
<tr>
<td>6</td>
<td>1997</td>
<td>NWT</td>
<td>SCID</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>1997</td>
<td>Manitoba</td>
<td>SCID</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>2003</td>
<td>Manitoba</td>
<td>SCID</td>
<td>***</td>
</tr>
</tbody>
</table>

* all eight cases died; all were First Nations infants except case 6 (an Inuit child)

** year of diagnosis not indicated in report

*** personal communication with Nancy Williamson, Sanitorium Board of Manitoba

The data in Table 1 represent the experience using BCG between 1996 and 2000 in British Columbia, Alberta, Saskatchewan, Manitoba, and northwestern Ontario.

During that time period, an estimated 14,622 doses were given, while three cases of disseminated BCG infection occurred in the same population (83, 95). Applying 95% confidence limits for rates which follow a poisson distribution (96), the estimated rate of disseminated BCG infections is 205 per million in these cohorts of vaccinated infants.
(95% C.I. 62, 678). Although the confidence interval is quite wide, the lower limit is more than 40 times higher than the estimated rate in European populations (66).

### 1.4 Decision analysis

Making decisions in medicine and public health can be relatively straightforward, if an affordable and safe treatment or intervention exists which clearly prevents disease, mortality, disability, and/or a poor quality of life. However, the development of alternative interventions, cost-effectiveness, and safety questions can all make decision-making more difficult. In response, quantitative methods have been developed to help solve difficult clinical decision problems. One such method is decision analysis, which compares the expected health outcomes of different intervention strategies in simulated cohorts (97). To do so, a decision tree is constructed in which members of each hypothetical cohort are exposed to a specific intervention, and may experience a number of health states afterwards. Probabilities for movement among different health states are affected by the natural histories of diseases in the model, and the intervention given to each cohort. Markov modelling is a technique that allows individuals in each simulated cohort to move into different health states throughout a series of time intervals referred to as cycles or stages. This approach is preferred for scenarios in which clinical decisions have long-term implications, multiple events over time are involved, and/or the probability of events change over time (98). Markov modelling is the superior option in evaluating the effectiveness of programs to prevent paediatric TB, due to the different states of tuberculous infection one may experience over time (primary infection, latent
infection, and reinfection) and the age-dependent risks of TB disease – particularly meningeal and miliary TB - among children (6, 17-19).

Decision analyses have been developed to estimate the effectiveness of BCG vaccine in preventing morbidity and mortality among health care workers (99, 100), the homeless (101), and HIV-infected adults (102). Rouillon and Waaler (103) created a decision model to compare the benefits and risks of BCG among infants assuming different risks of tuberculous infection and breakdown to disease. The assumed risk of disseminated BCG infection in the model was quite low (one per 10,000,000 vaccinated newborns). More recently, a Markov model was developed to examine the effectiveness of BCG among cohorts of infants in Finland (104). This study did not consider the risk of disseminated BCG infection. To date, no study has considered the impact of SCID incidence at birth, and quality of life among children with permanent sequelae following tuberculous meningitis, on BCG policy decisions.
2 OBJECTIVES

There were four main objectives in this study: 1) to establish utility values for acute TB states and the state of permanent neurological sequelae following acute tuberculous meningitis; 2) to estimate the future burden of illness in cohorts of children in which a neonatal BCG program is present or absent; 3) to estimate threshold values for the incidence of SCID at birth, above which the decision to give BCG is no longer supported by the model; and 4) to assess the robustness of results to changes in the values for key variables in the model.
3 METHODS

3.1 Structure of decision model

A state-transition, Markov model was developed to predict the benefits and risks of BCG in Aboriginal infants under varying epidemiologic conditions. Analyses were done for theoretical populations experiencing different risks of tuberculous infection, and different risks of SCID in newborns. The Markov model was constructed using DATA 4.0 software (TreeAge Software, Inc., Williamstown, MA). Similar to Rouillon and Waaler (103) and Hersh et al. (104), the model followed cohorts throughout childhood (birth to 14 years). The cycle length was six months, due to several assumptions described below.

3.1.1 Intervention

The model compared a control scenario (no BCG vaccination) to intervention with BCG vaccine. The decision model for the period from birth to age six months is depicted in Figure 1. Model branches and subtrees were identical for both BCG program options, and probabilities for movement into different states affected by vaccination (disseminated BCG infection and tuberculosis disease states) were linked between cohorts using expressions of relative risk (105).
Figure 1. Decision model for BCG vaccination at birth to age six months

* Death due to disseminated BCG infection
** Death due to SCID
*** Death due to unrelated causes
**** Individual moves to TB disease state (either meningeal, miliary, or other forms of TB) in the next cycle of the model (age 6-12 months)

3.1.2 Markov health states

Health states in the Markov model beyond the age of six months (after the first cycle) are shown in Figure 2. Uninfected children remain well until the last stage in the model, unless primary tuberculous infection or death due to unrelated causes intervene. Children with primary infection may progress to disease or move into the latent infection state. Children with latent infection may experience exogenous reinfection (exposure to a new strain of \textit{M. tuberculosis}). Reinfected individuals who do not develop disease return once again to the latent infection state.
Figure 2. Markov health states after the first cycle in the model

* Death due to unrelated causes
** Death due to acute TB states
*** Individual moves to TB disease state in the next Markov cycle
Proportions of uninfected children who experience primary infection, and latently infected children who experience exogenous reinfection, depend on the annual risk of tuberculous infection (the ARI). This represents the overall proportion of the total population infected with \textit{M. tuberculosis} each year.

Children in all three infection states described above may develop TB disease. Among those who develop disease, three states are possible: TB of the central nervous system (CNS) and meninges (ICD-9 013); miliary tuberculosis (ICD-9 018), and non-meningeal, non-miliary TB. The latter state includes all forms of TB disease (including primary and respiratory disease) with ICD-9 codes other than 013 or 018. TB of the CNS and meninges is referred to as “meningeal TB” or “tuberculous meningitis” throughout the report. Children with meningeal TB may develop permanent neurological sequelae. All children with acute TB who do not die or experience disability move into the latent infection state.

\textbf{3.2 Assumptions}

Several assumptions were made in the model. First, the theory that BCG protects against primary infection and endogenous reactivation, but not against exogenous reinfection, is applied in the model (58). The state of SCID lasted one cycle, through the first six months of life. This is based on a review that found that the median age at which infants receive a bone marrow transplant (BMT) is approximately six months (106). Since SCID is fatal among infants who do not receive a successful BMT (74), infants with this disorder can move into two possible states at age six months: death; or
uninfected. Therefore, it is assumed that children who receive a successful BMT experience a normal state of health afterwards (74). It is also assumed that exposure of SCID patients to tuberculous infection (the risk of infection with \textit{M. tuberculosis}) is nil during the first stage of the model (Figure 1). This was done to simplify the structure of the model. Data on TB outcomes among patients with SCID is lacking. Even if exposure was included, it would be equal in both cohorts, meaning risk/benefit outcomes would remain unchanged. Furthermore, it would have a negligible impact on predicted TB disease rates in each cohort, as the overall risk of having SCID, being exposed to \textit{M. tuberculosis}, and then developing TB disease, is quite low.

The model makes the conventional assumption that once infected with \textit{M. tuberculosis}, an individual remains infected for life (1). The primary infection and reinfection states are also assumed to last six months, after which individuals develop TB disease or move into the latent infection state. This time period was chosen because children who develop miliary or meningeal TB generally do so three to six months following initial exposure to bacilli (16, 21). Similarly, TB disease states are assumed to last one stage (six months) in the model, due to the availability of short-course, six-month regimens for TB treatment. This is a simplifying assumption: it is recognized that TB cases are often found several months after the onset of disease; and that regimens for treatment of extrapulmonary disease are usually longer than six months (21). Finally, all forms of TB other than miliary disease and tuberculous meningitis have been grouped into a single state (non-meningeal, non-miliary TB). Evidence for the protective effects of BCG among infants and children has been fairly specific to either all forms of TB disease (27), or miliary and meningeal disease (26).
3.3 Input data

Effectiveness and adverse effects of BCG were estimated from published meta analyses, case series reviews and other studies. Probability estimates and utility values were based on case series and administrative data specific to Canadian Aboriginal populations, if available. When necessary, six-month transition probabilities in the model \( R_{6} \) were estimated from annual (12-month) risk values \( R_{12} \) with the expression (107):

\[
R_{6} = 1 - (1 - R_{12})^{1/2}
\]

For example, if the assumed ARI is 1%, the six-month risk of tuberculous infection in the model is approximately 0.5013%.

To estimate a utility value for the state of permanent neurological sequelae following tuberculous meningitis, subjects were recruited to participate in an interview involving the standard gamble technique. During the interview, subjects were offered two alternatives, the first of which was the possibility of perfect health for the remainder of life with a probability of immediate death, and the second of which was living the rest of life with permanent sequelae from tuberculous meningitis. The probability of death was varied between 0 and 1 until the individual was indifferent between the alternatives, and the utility score for the health state in question became one minus that probability. This technique obeys the fundamental axioms of utility theory, giving the respondent a choice and introducing the element of uncertainty (108, 109).

A computer tool developed in Excel 2000 software (Microsoft, Inc., Redmond, WA) was used during the interviews, in which the two alternatives in the standard gamble were shown to the subject (see Appendix 1). The probability of immediate death for "choice A" was first set to 90%, by entering an invisible (white font) value in the box...
at the bottom left-hand corner. The probability was automatically reflected in both the shading of the pie chart (the black area indicating the probability of death) and the number of patients who survive or die in the example on the right-hand side. If the respondent opted for “choice A,” the response was marked as 0.05. If the chronic health state was chosen, the probability of death was reduced to 10%, and the exercise was repeated. If “choice A” was selected, the probability of death was increased to 80%, and so on, until a threshold of indifference (described above) was found (109).

Before completing the exercise for the state of permanent sequelae following tuberculous meningitis, two examples were done. The states involved in these examples were blindness in one eye, and then blindness in both eyes. If the participant accepted a higher risk of death (thus having a lower utility score) for blindness in one eye than for blindness in both eyes, it was assumed that the individual had a poor understanding of the exercise and the interview was terminated.

The description of the health state for permanent sequelae following tuberculous meningitis (see Appendix 2) consisted of a brief text describing important elements of the state, followed by descriptors from the Health Utility Index (HUI) Mark III. The HUI Mark III is a multi-attribute classification system, which was validated in a Canadian population (109). The brief text was based on a review of 180 patients with tuberculous meningitis in India (110). This study found that 39% of patients had neurological sequelae, and among these the majority were considered to have “moderate residual damage” (hemiparesis, involuntary movements, and substantial mental impairment). Rarer complications such as blindness, deafness, and hypopituitarism (111, 112) were not included. Two physicians were asked to provide feedback and input in developing the
description: first, a respirologist and author of the chapter on extrapulmonary TB in the Canadian Tuberculosis Standards (113); and second, a neurologist from the Ottawa Hospital. During the interview, the health state was described as “Condition X.”

The sample size calculation for the number of participants required assumed a standard deviation of 0.3, as recommended when obtaining utility estimates from the general public (108). A sample size of 100 participants results in a predicted 95% confidence interval of 0.0588. Assuming this was an appropriate range for sensitivity analyses, a minimum sample size of 100 participants was sought. The mean utility value from the sample was used as the parameter estimate in the model, as recommended by Torrance et al. (114). A range for variability and uncertainty analyses was obtained by calculating 95% confidence limits.

Ethical approval for the interview process was sought and obtained from the Ottawa Hospital Research Ethics Board (OHREB). Signed written consent for participation in the study was obtained from subjects before starting the interview. The letter of approval from the OHREB, and the consent form for participants, are presented in Appendices 3 and 4, respectively. Volunteers for interviews were recruited from three groups: first-year medical students at the University of Ottawa (year of entrance 2002); employees at FNIHB Headquarters, Ottawa; and staff at the Department of Social Development and Health, Mohawk Council of Akwesasne. A letter of permission from the Health Director at Akwesasne is shown in Appendix 5. The rationale for interviewing volunteers from these groups was both to interview three separate groups from the general public (in other words neither patients with TB-related sequelae or their physicians); and to oversample Canadians of Aboriginal origin. People from the general
public were interviewed because the decision to give BCG represents a public policy issue, rather than that of individual community members (115, 116). Members of a First Nations community were included, because the only routine BCG programs in Canada are delivered in First Nations and Inuit communities. Evidently, this strategy did not achieve a random sample of the general population. For this reason, analyses were done to assess the effects of factors such as group, sex, level of education, age, and parental status on utility scores. These data were collected from individuals prior to the interview, and entered into an Access (Microsoft, Inc., Redmond, WA) database. The data were later exported to SPSS® 11.0 (SPSS Inc., Chicago, IL) for statistical analyses. Mean utility scores and 95% confidence limits were calculated for different relevant groupings, and a linear regression analysis was done to assess the effect of age on utility scores.

3.4 Outcomes

Base case and Markov cohort analyses were completed for four hypothetical cohorts, experiencing different BCG programs and risks of tuberculous infection. Two of the cohorts (unvaccinated controls and those receiving BCG) were exposed to an ARI of 1%, while the other two cohorts were exposed to an ARI of 0.1%. These analyses were carried out using the base probability and utility values in the model, with the incidence of SCID among newborns set to 0.

Outcomes measured in base case analyses were life expectancy, quality-adjusted life expectancy (QALYs), and discounted QALYs. Future QALYs were discounted at a rate of three percent, as recommended by the Panel on Cost-Effectiveness in Health and
Medicine (117). In Markov cohort analyses, the probability of individuals being in each state in each year of the model was estimated. These analyses were done in DATA 4.0 software (TreeAge Software, Inc., Williamstown, MA), and exported to Excel 2000 software (Microsoft, Inc., Redmond, WA) for graphing. TB case tallies (all forms, meningeal, miliary, and children with neurological sequelae) and fatalities were estimated in each cohort, assuming a birth cohort of 100,000.

3.5 Variability and uncertainty analyses

Variability was assessed using sensitivity analyses. Upper and lower values for sensitivity analyses were obtained using several strategies: 95% confidence limits from a meta-analysis were used; 95% confidence limits were calculated for proportions (probabilities estimated from administrative data); an interquartile range was estimated for non-normally distributed data; or a range of values from published reports were used. For probabilities near 0, exact binomial 95% confidence limits were calculated (118).

To evaluate the impact of SCID on the decision to use BCG, the threshold incidence of SCID above which BCG is not supported by the model (above which BCG reduces quality-adjusted life expectancy) was first calculated assuming an ARI of 0.1%. The robustness of this threshold value was assessed by varying single parameters across their ranges in one-way sensitivity analyses. Two-way sensitivity analyses were then carried out on the ARI and SCID incidence at birth, to estimate threshold values across a range of risks for tuberculous infection (0.1 – 1%). Finally, three-way sensitivity
analyses were done to assess the effects of simultaneously varying the parameters which the above threshold values were most sensitive to.

Uncertainties in probability and utility values in the model were assessed using probabilistic Monte Carlo simulation (119, 120). In this method, probability and utility values are assigned distributions, the means of which equal base values for parameter estimates. Multiple simulations are run, in which parameters are randomly assigned values within their distributions. The utility value for neurological sequelae was assigned a normal distribution. Variables estimated from a range of published reports, or a median and interquartile range, were assigned triangular distributions. Empiric probability variables (e.g. TB case fatality estimates) were assigned β distributions (119). A range of outcomes (mean discounted QALYs and 95% confidence limits) was generated for each of the four cohorts described in the previous section.

First, Monte Carlo simulations were done for cohorts in which the risk of SCID is 0. These analyses were then repeated assuming increasing risks of SCID in the population. The risk of SCID was varied from one to 50 per 100,000 births, the approximate risks reported in three European populations (75-77) and a North American Aboriginal population (83), respectively. The objective of this exercise was to compare quality-adjusted life expectancy in vaccinated and unvaccinated cohorts at all rates of SCID incidence between one and 50 per 100,000. Differences in outcomes between cohorts (vaccinated and unvaccinated) were considered statistically significant if 95% confidence limits did not overlap.
4 RESULTS

4.1 Probability estimates

Probabilities for movement between states in the model are shown in Table 3. The relative risk of primary infection among vaccinated children was estimated from published studies on BCG vaccination in three Canadian First Nations populations (53, 90, 91). In vaccinated children who are infected, additional protection against meningeal and miliary TB was estimated from two meta-analyses (26, 27).

The risk of disseminated BCG infection was based on a review of 38 infants in France who were born with SCID and received BCG vaccine (77). Case fatality estimates for infants with disseminated BCG infection were drawn from a case series review (71) and surveillance study (66). The probability of death due to SCID among unvaccinated infants was based on studies of bone marrow transplant success in Canada (80), the United States (121), and a North American Aboriginal population (81).

The ARI was varied from 0.1% to 1% in analyses, as described above. Based on data from a Canadian First Nations population, the ARI in the model declined at a rate of 13.8% per year (8). This is identical to the rate of decline observed in the Dutch population between 1940 and 1970 (5), and only slightly higher than the estimated rate of decline in Saskatchewan (11–12% per year) during the 1954-1971 period (122). The rate of decline was lowered to 0% to simulate poorly controlled, endemic TB, in sensitivity analyses.
Estimates of the risks of disease following primary infection, reactivation of latent infection, and disease following reinfection were based on a study in which maximum likelihood methods were used to fit model predictions of disease incidence to TB notifications in a Canadian First Nations population (8). These methods are similar to those of Sutherland et al. applied to the Dutch population (5). The assumed range of risks for primary disease (14-30%), is similar to published estimates for the risk of TB following infection in children (15, 16).

The probabilities of developing meningeal and miliary TB among children with TB disease were estimated using a review of pediatric TB cases in California (19). The distribution of cases by main diagnostic site for 4607 TB notifications aged 0-14 years during the 1985-1995 period was reviewed in this study. The estimated risk of tuberculous meningitis following primary infection in the model was compared to results from other studies. Given a 22% risk of primary disease (8), and a 4% risk of meningitis if disease develops (19), the risk of meningeal TB following primary infection among 0-4 year olds in the model is 0.88%. In a study from South Africa, it was estimated that 0.5% of children with tuberculous infection in the 0-4 year age group go on to develop tuberculous meningitis (123). The corresponding estimate from studies in four European populations was approximately 1% (124-127). The risk of neurological sequelae following acute tuberculous meningitis was derived from a Canadian case series review including several First Nations patients (128).

Risks of case fatality were estimated using a case-level data set of all reported TB cases (2706) in the Canadian First Nations population (living on and off reserve) between 1990 and 2000 (unpublished data, Population and Public Health Branch, Health Canada).
On the standard Canadian case report form for TB, there are two fields for mortality. The first indicates whether the patient lived or died, while the second stratifies deaths by those caused directly by TB, those in which TB was not the main cause but a contributing factor, and those in which TB played no role. In this study, only cases in which TB was considered the cause of death, or TB was not the primary cause but contributed to the death, were considered case fatalities. Vital status was reported among 2550 (94%) of the 2706 First Nations TB cases included in the data set. Overall TB case fatality was 4% (Table 4). Seven cases of miliary disease and five cases of tuberculous meningitis were reported among children aged 0-14 years between 1990 and 2000. Although none of these children died, overall case fatality rates for those conditions were 29% and 9%, respectively. One child (0.12%) out of 803 cases in the 0-14 year age group died, due to congenital TB. Case fatality was much higher in adults (6%). Age-specific risks of mortality due to unrelated causes (causes other than SCID, BCG infection, or TB) were estimated using 1999 mortality rates from the First Nations, on-reserve population (129).
Table 3. Input data for Markov model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (range)</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual risk of tuberculous infection</td>
<td>(0.001-0.01)</td>
<td>Assumed</td>
</tr>
<tr>
<td>Annual rate of decline in the risk of infection</td>
<td>0.14 (0.0-0.14)</td>
<td>8</td>
</tr>
<tr>
<td>Relative risk of primary infection if vaccinated(^a)</td>
<td>0.39 (0.20-0.43)</td>
<td>53, 90, 91</td>
</tr>
<tr>
<td>Relative risk of meningeal or miliary TB if vaccinated(^a)</td>
<td>0.14 (0.05-0.35)</td>
<td>26, 27</td>
</tr>
<tr>
<td>Risk of TB following primary infection(^a)</td>
<td>0.22 (0.14-0.30)</td>
<td>5, 8, 15, 16</td>
</tr>
<tr>
<td>Risk of TB due to reactivation(^a)</td>
<td>0.0009 (0.0008-0.001)</td>
<td>5, 8</td>
</tr>
<tr>
<td>Risk of TB following exogenous reinfection(^a)</td>
<td>0.058 (0.028-0.092)</td>
<td>5, 8</td>
</tr>
<tr>
<td>Proportion of TB cases with meningeal TB (0-4 years)</td>
<td>0.040 (0.033-0.047)</td>
<td>19</td>
</tr>
<tr>
<td>Proportion of TB cases with meningeal TB (5-14 years)</td>
<td>0.015 (0.006-0.020)</td>
<td></td>
</tr>
<tr>
<td>Risk of neurological sequel from meningeal TB(^a)</td>
<td>0.29 (0.13-0.39)</td>
<td>110, 128, 130</td>
</tr>
<tr>
<td>Proportion of TB cases with miliary TB (0-4 years)</td>
<td>0.0086 (0.0050-0.012)</td>
<td>19</td>
</tr>
<tr>
<td>Proportion of TB cases with miliary TB (5-14 years)</td>
<td>0.0055 (0.0015-0.01)</td>
<td></td>
</tr>
<tr>
<td>Risk of disseminated BCG infection among vaccinated infants born with SCID(^b)</td>
<td>0.36 (0.19-0.56)</td>
<td>77</td>
</tr>
<tr>
<td>Risk of fatality from meningeal TB(^b)</td>
<td>0.091 (0.030-0.15)</td>
<td>Health Canada data</td>
</tr>
<tr>
<td>Risk of fatality from miliary TB(^b)</td>
<td>0.29 (0.23-0.36)</td>
<td></td>
</tr>
<tr>
<td>Risk of fatality from other forms of TB(^b)</td>
<td>0.0013 (0.0013-0.007)</td>
<td></td>
</tr>
<tr>
<td>Risk of fatality, unvaccinated infants with SCID(^a)</td>
<td>0.25 (0.19-0.33)</td>
<td>80, 81, 121</td>
</tr>
<tr>
<td>Risk of fatality, disseminated BCG infection(^a)</td>
<td>0.87 (0.8-0.97)</td>
<td>66, 71</td>
</tr>
<tr>
<td>Utility value for severe combined immunodeficiency</td>
<td>0.5 (0.25-0.75)</td>
<td>Assumed</td>
</tr>
<tr>
<td>Utility value for acute meningeal TB(^a)</td>
<td>0.93 (0.81-0.95)</td>
<td>Manitoba hospital data</td>
</tr>
<tr>
<td>Utility value for miliary TB(^a)</td>
<td>0.92 (0.69-0.97)</td>
<td></td>
</tr>
<tr>
<td>Utility value for other forms of TB(^a)</td>
<td>0.98 (0.97-0.98)</td>
<td></td>
</tr>
<tr>
<td>Utility value for neurological sequel following acute meningeal TB(^a)</td>
<td>0.43 (0.37-0.49)</td>
<td>Survey</td>
</tr>
</tbody>
</table>

Distributions in Monte-Carlo simulations: \(^a\) triangular; \(^b\) \(\beta\); \(^c\) normal
Table 4. Number of total TB cases and case fatality rate among First Nations people in Canada, by age and disease site (1990-2000)*

<table>
<thead>
<tr>
<th>Disease site</th>
<th>0-14 years</th>
<th>15+ years</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS TB</td>
<td>5 (0.0%)</td>
<td>39** (10.3%)</td>
<td>44 (9.1%)</td>
</tr>
<tr>
<td>Miliary TB</td>
<td>7 (0.0%)</td>
<td>85** (31.8%)</td>
<td>92 (29.3%)</td>
</tr>
<tr>
<td>TB (other forms)</td>
<td>791 (0.13%)</td>
<td>1630 (4.5%)</td>
<td>2421 (3.1%)</td>
</tr>
<tr>
<td>TB (all forms)</td>
<td>803 (0.12%)</td>
<td>1747 (6.0%)</td>
<td>2550 (4.1%)</td>
</tr>
</tbody>
</table>

* case fatality rate shown in brackets  
** 7 cases were diagnosed with both CNS and miliary TB

4.2 Utility values for tuberculosis states

Utility values for health states in the model are shown in Table 3. Values for the three forms of acute tuberculosis were estimated using hospitalization data from a computerized provincial discharge file provided by Manitoba Health. The median duration of hospitalization was given a utility value of zero, and this time period was subtracted from 182.625 (the number of days in six months) to obtain a utility value for the six-month acute TB state (131). Analyses are shown in Table 5. The median duration of hospitalization for all TB cases was 15.5 days. Among acute miliary and meningitis cases (all ages), the median lengths of stay were 14.5 and 13 days, respectively. The median duration for children with TB (all forms) aged 0-14 years was three days.
Table 5. Number of total TB hospitalizations and median duration of stay* among
Manitoba First Nations people, by age and disease site (fiscal years 1990/1991 -
1999/2000)

<table>
<thead>
<tr>
<th>Site of first diagnosis</th>
<th>Age group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-14 years</td>
<td>15+ years</td>
<td>All ages</td>
</tr>
<tr>
<td>CNS TB</td>
<td>2</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Miliary TB</td>
<td>0</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>TB (other forms)</td>
<td>27</td>
<td>371</td>
<td>398</td>
</tr>
<tr>
<td>TB (all forms)</td>
<td>3 (3-4)</td>
<td>16 (7-29)</td>
<td>16 (6-28)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>407</td>
<td>436</td>
</tr>
<tr>
<td></td>
<td>3 (3-5.5)</td>
<td>16 (7-30)</td>
<td>15.5 (6-29)</td>
</tr>
</tbody>
</table>

* median duration of stay in days shown in second row of each cell (interquartile range in brackets)

A total of 107 individuals were interviewed in the survey. Four interviews were
terminated due to lack of comprehension. Thirty-seven medical students, 34 FNIHB
employees, and 32 employees at the Akwesasne Department of Social Development and
Health completed the interview. The age range of respondents was 20 to 58 years. The
mean age of the sample was equal to the median age (35 years old). Most of the
respondents were female (71%). Approximately half of the sample reported having at
least one university degree, and 51% of the respondents had one or more children.

Mean values for blindness in one eye and blindness in both eyes were 0.76 (95% CI 0.71, 0.80), and 0.59 (95% CI 0.54, 0.65), respectively. The overall mean utility value
for neurological sequelae following tuberculous meningitis was 0.43 (95% CI 0.37, 0.49).
Mean utility scores for neurological sequelae, stratified by interview group, sex, level of
education, parental status, and age group, are shown in Table 6.
Table 6. Mean utility scores for neurological sequelae following acute meningeal TB, by group, sex, level of education, parental status, and age group

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample size</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>103</td>
<td>0.43 (0.37, 0.49)</td>
</tr>
<tr>
<td>Medical students</td>
<td>37 (36%)</td>
<td>0.46 (0.37, 0.55)</td>
</tr>
<tr>
<td>FNIHB employees</td>
<td>34 (33%)</td>
<td>0.42 (0.31, 0.53)</td>
</tr>
<tr>
<td>Akwasasne</td>
<td>32 (31%)</td>
<td>0.41 (0.29, 0.53)</td>
</tr>
<tr>
<td>Male</td>
<td>30 (29%)</td>
<td>0.42 (0.32, 0.53)</td>
</tr>
<tr>
<td>Female</td>
<td>73 (71%)</td>
<td>0.43 (0.36, 0.51)</td>
</tr>
<tr>
<td>No university</td>
<td>50 (49%)</td>
<td>0.46 (0.37, 0.55)</td>
</tr>
<tr>
<td>University</td>
<td>53 (51%)</td>
<td>0.40 (0.33, 0.48)</td>
</tr>
<tr>
<td>No children</td>
<td>50 (49%)</td>
<td>0.44 (0.36, 0.53)</td>
</tr>
<tr>
<td>One or more children</td>
<td>53 (51%)</td>
<td>0.42 (0.33, 0.50)</td>
</tr>
<tr>
<td>0-34 years old</td>
<td>50 (49%)</td>
<td>0.47 (0.38, 0.55)</td>
</tr>
<tr>
<td>35 years or older</td>
<td>53 (51%)</td>
<td>0.40 (0.31, 0.48)</td>
</tr>
</tbody>
</table>

The mean utility scores did not differ significantly across any of the groups in Table 6. They varied from 0.40 to 0.47, all within the 95% confidence limits of the overall mean. The mean value among people from Akwasasne was 0.41 (95% CI 0.29, 0.53), compared with 0.46 (95% CI 0.37, 0.55) among medical students and 0.42 (95% 0.31, 0.53) among FNIHB employees. Female and male respondents had almost identical mean values (0.43 and 0.42, respectively). Age was not a significant predictor of utility scores, according to linear regression analysis (p = 0.36).
4.3 Base case analysis

Life expectancy, QALY, and discounted QALY outcomes - assuming the incidence of SCID is 0 - are summarized in Table 7.

Table 7. Estimated life expectancy, QALYs, and discounted QALYs, by ARI and BCG program decision (birth to age 14 years)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1% ARI</th>
<th></th>
<th>0.1% ARI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No BCG</td>
<td>BCG</td>
<td>No BCG</td>
<td>BCG</td>
</tr>
<tr>
<td>Discounted QALYs</td>
<td>11.67284</td>
<td>11.67389</td>
<td>11.67401</td>
<td>11.67412</td>
</tr>
</tbody>
</table>

4.4 Markov cohort analyses

Markov cohort analyses for populations experiencing 1% and 0.1% annual risks of infection are shown in Figures 3 and 4, respectively. These analyses depict the natural history of TB in the population, in the absence of BCG vaccine and SCID. Figure 3 shows that 1% of children receive a primary infection during their first year of life, while 0.1% are infected during the first year in Figure 4. The proportion of children with primary infection decreases over time as the ARI declines, and exogenous reinfections increase. The proportions of children living with latent tuberculous infection and permanent sequelae following acute meningeal TB increase over time.
Figure 3. Markov cohort analysis with an ARI of 1%, in the absence of BCG vaccine and SCID
Figure 4. Markov cohort analysis with an ARI of 0.1%, in the absence of BCG vaccine and SCID
4.5 Estimations of the burden of disease and deaths caused by TB

Model predictions of the total number of TB cases (all forms, meningeal, and miliary), children with neurological sequelae, and TB case fatalities, are summarized in Table 8. If the ARI is 1%, BCG prevents 961 total TB cases and six deaths in a cohort of 100,000 children, during the 15-year period. In the same cohort, 38 cases of meningeal TB and nine cases of miliary TB would be prevented by BCG. According to the model, the vaccine prevents the occurrence of neurological sequelae in nine children.

Table 8. Estimated TB case tallies and deaths in a birth cohort of 100,000, by ARI and BCG program decision (birth to age 14 years)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1% ARI</th>
<th></th>
<th>0.1% ARI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No BCG</td>
<td>BCG</td>
<td>No BCG</td>
<td>BCG</td>
</tr>
<tr>
<td>Tuberculosis (all forms)</td>
<td>1571</td>
<td>610</td>
<td>160</td>
<td>60</td>
</tr>
<tr>
<td>Meningeal TB</td>
<td>44.7</td>
<td>6.4</td>
<td>4.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Miliary TB</td>
<td>11.3</td>
<td>1.6</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Neurological sequelae</td>
<td>13.0</td>
<td>2.0</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>TB-related deaths</td>
<td>7.3</td>
<td>1.1</td>
<td>0.7</td>
<td>0.1</td>
</tr>
</tbody>
</table>

If the ARI is 0.1%, the vaccine prevents 100 TB cases, while the total number of TB deaths in a cohort of 100,000 is less than one regardless of the BCG program decision. Over the 15-year period, the cumulative incidence of neurological sequelae is
0.2 per 100,000 with a BCG vaccination program, and one per 100,000 if the vaccine is not given.

Figures 5 shows the predicted rates of TB (all forms of disease) in four cohorts from birth to age 14 years. The rates decrease in all groups as the ARI declines over time. If the ARI is 1%, the TB rate is over 200 per 100,000 in the first year of life without a BCG program.

Model predictions of meningeal and miliary TB rates are shown in Figures 6 and 7, respectively. Declines in rates reflect both the decreasing ARI, and the lower risks for these forms of disease among children aged five years or more (Table 3). The rate of tuberculous meningitis is eight per 100,000 in the first year of life, if the ARI is 1% and no vaccine is given. BCG reduces the rate to approximately one per 100,000. If the ARI is 0.1%, annual rates remain below one per 100,000, regardless of the vaccination policy.

During the first five years of life, the rate of miliary disease exceeds one per 100,000 if the ARI is 1% and no BCG is given (Figure 7). Rates in all other cohorts remain lower than one per 100,000 throughout the 15-year period.

Figure 8 depicts the accumulation of children with permanent neurological sequelae following acute tuberculous meningitis. If the ARI is 1% and no BCG is given, a total of 13 cases is predicted in a cohort of 100,000 children over 15 years. Eight of the 15 cases occur before the age of five years. The rate is less than one per 100,000 in BCG vaccinated and unvaccinated cohorts, if the ARI is 0.1%.
Figure 5. Estimated TB rate (all forms), by BCG program decision and ARI (%)
Figure 6. Estimated meningeal TB rate, by BCG program decision and ARI (%)
Figure 7. Estimated miliary TB rate, by BCG program decision and ARI (%)
Figure 8. Estimated cumulative incidence of neurological sequelae, by BCG program decision and ARI (%)
4.6 Variability and uncertainty analyses

If the ARI is 0.1%, the threshold value for SCID incidence – above which BCG is not supported by the model - is 4.2 per 100,000 births. The effects of varying other parameters on this threshold are summarized in Table 9. The threshold was not altered to more than 8.0 per 100,000, or to less than two per 100,000, by varying any of the parameters. The threshold was most sensitive to the risk of disseminated BCG infection among vaccinated infants born with SCID. Assuming the lower limit of risk (19%) increases the threshold to 8.0 per 100,000, while increasing the risk to 56% reduces the threshold to 2.7 per 100,000. When the annual rate of decline in the ARI is set to 0, the threshold increases to 6.1 per 100,000. Reducing the risk of TB disease following primary infection to 14% decreases the threshold to 2.8 per 100,000. Varying the utility value for neurological sequelae across the range estimated in this study had little effect on the threshold.

Results of the two-way sensitivity analysis on ARI and SCID incidence are shown in Figure 9. If the ARI is increased to 1%, the threshold value for SCID is 41 per 100,000 births.

Figure 10 shows a three-way sensitivity analysis on the incidence of SCID, the risk of disseminated BCG infection among vaccinated infants with SCID, and the risk of TB disease following primary infection. In these analyses, the ARI is 0.1% (similar to the analyses presented in Table 9). Thresholds for SCID at which the decision to give BCG is altered are within 0 and 10 per 100,000 births in all scenarios.
Table 9. Effects of varying parameter estimates on the threshold SCID incidence at birth* in a population with an ARI of 0.1%

<table>
<thead>
<tr>
<th>Variable **</th>
<th>Base value</th>
<th>Range of values</th>
<th>SCID threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Annual rate of decline in the risk of infection</td>
<td>0.14</td>
<td>0.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Relative risk of primary tuberculous infection among children vaccinated with BCG</td>
<td>0.39</td>
<td>0.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Relative risk of meningeal or miliary TB among children vaccinated with BCG</td>
<td>0.14</td>
<td>0.05</td>
<td>0.35</td>
</tr>
<tr>
<td>Risk of TB disease following primary infection</td>
<td>0.22</td>
<td>0.14</td>
<td>0.30</td>
</tr>
<tr>
<td>Risk of neurological sequel following acute meningeal TB</td>
<td>0.29</td>
<td>0.13</td>
<td>0.39</td>
</tr>
<tr>
<td>Risk of disseminated BCG infection among vaccinated infants born with SCID</td>
<td>0.36</td>
<td>0.19</td>
<td>0.56</td>
</tr>
<tr>
<td>Risk of fatality from meningeal TB</td>
<td>0.091</td>
<td>0.030</td>
<td>0.15</td>
</tr>
<tr>
<td>Risk of fatality from miliary TB</td>
<td>0.29</td>
<td>0.23</td>
<td>0.36</td>
</tr>
<tr>
<td>Risk of fatality among unvaccinated infants with SCID</td>
<td>0.25</td>
<td>0.19</td>
<td>0.33</td>
</tr>
<tr>
<td>Risk of fatality from disseminated BCG infection</td>
<td>0.87</td>
<td>0.8</td>
<td>0.97</td>
</tr>
<tr>
<td>Utility value for neurological sequel following acute meningeal TB</td>
<td>0.43</td>
<td>0.37</td>
<td>0.49</td>
</tr>
</tbody>
</table>

* assuming the base values in Table 3 the threshold for SCID is 4.2 per 100,000
** parameters that did not alter threshold by 0.1 per 100,000 not shown
Figure 9. Two-way sensitivity analysis on the assumed ARI (%) and incidence of SCID at birth in the population.
Risk of disseminated BCG infection

Figure 10. Three-way sensitivity analysis on the risks of primary TB, BCG infection among vaccinated infants with SCID, and SCID at birth (ARI = 0.1%)
Table 10. Results of Monte Carlo simulations, assuming different risks of SCID in neonates

<table>
<thead>
<tr>
<th>Discounted QALYs and 95% confidence limits</th>
<th>1% ARI</th>
<th>0.1% ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No BCG</td>
<td>BCG</td>
</tr>
<tr>
<td>Risk of SCID: 0 per 100,000 births</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.67284</td>
<td>11.67389*</td>
</tr>
<tr>
<td>Lower 95% confidence limit</td>
<td>11.67188</td>
<td>11.67363</td>
</tr>
<tr>
<td>Upper 95% confidence limit</td>
<td>11.67355</td>
<td>11.67404</td>
</tr>
<tr>
<td>Risk of SCID: 1 per 100,000 births</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.67278</td>
<td>11.67382*</td>
</tr>
<tr>
<td>Lower 95% confidence limit</td>
<td>11.67174</td>
<td>11.67355</td>
</tr>
<tr>
<td>Upper 95% confidence limit</td>
<td>11.67349</td>
<td>11.67398</td>
</tr>
<tr>
<td>Risk of SCID: 25 per 100,000 births</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.67197</td>
<td>11.67238</td>
</tr>
<tr>
<td>Lower 95% confidence limit</td>
<td>11.67103</td>
<td>11.67195</td>
</tr>
<tr>
<td>Upper 95% confidence limit</td>
<td>11.67270</td>
<td>11.67274</td>
</tr>
<tr>
<td>Risk of SCID: 50 per 100,000 births</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.67109</td>
<td>11.67089</td>
</tr>
<tr>
<td>Lower 95% confidence limit</td>
<td>11.67015</td>
<td>11.67018</td>
</tr>
<tr>
<td>Upper 95% confidence limit</td>
<td>11.67186</td>
<td>11.67158</td>
</tr>
</tbody>
</table>

* outcome is significantly higher for this decision (95% confidence limits for outcomes among vaccinated and unvaccinated cohorts do not overlap)
Results of the Monte Carlo simulations are shown in Table 10. If the risk of SCID is 0, discounted QALYs are significantly increased by BCG vaccine regardless of the assumed ARI.

If the ARI is 0.1%, quality-adjusted life expectancy is not significantly improved by BCG unless there is no SCID occurring in the population. If the risk of SCID is 23 per 100,000 births or higher, BCG is contraindicated (Table 11). SCID did not significantly reduce quality-adjusted life expectancy among BCG-vaccinated children at any level of risk (from one to 50 per 100,000 births), if the ARI was 1%. BCG significantly increases quality-adjusted life expectancy if the risk of SCID is one per 100,000 births, and the ARI is 1%. However, there is no significant difference in outcomes if the risk of SCID is five per 100,000 births or higher (Table 11).

**Table 11.** Threshold values of SCID incidence estimated from Monte-Carlo simulations

<table>
<thead>
<tr>
<th>Thresholds of SCID incidence (per 100,000)</th>
<th>Annual risk of tuberculous infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>0</td>
<td>BCG</td>
</tr>
<tr>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>23</td>
<td>No BCG</td>
</tr>
</tbody>
</table>

BCG: QALE significantly higher among vaccinated; NS: no significant difference in QALE between cohorts; No BCG: QALE significantly higher among unvaccinated; if ARI = 1%, threshold SCID incidence at which BCG contraindicated is higher than 100 per 100,000.
5 DISCUSSION

5.1 Summary of findings

Results of this study show clear benefits from BCG vaccination when the risk of tuberculous infection is 1% per year. The model estimates that 961 TB cases would be prevented by BCG in a cohort of 100,000, over a 15-year period. Assuming approximately 3000 First Nations infants are vaccinated each year (this report), 29 additional TB cases would occur with no BCG program. It is also evident that BCG plays an important role in preventing disability when the risk of infection is elevated (Figure 8). These findings are consistent with other analyses (103, 132) and recommendations for the use of BCG in North American populations (133, 134).

If the ARI is 0.1%, the benefits are less clear. Rates of severe TB disease and deaths are quite low (lower than one per 100,000 per year and 0.1 per 100,000 per year, respectively) regardless of the BCG vaccination policy. The threshold for risk of SCID above which BCG is not required (4.2 per 100,000 births) is only slightly higher than the incidence reported in three European populations (75-77). Results of this study are therefore consistent with recommendations of the International Union against Tuberculosis and Lung Disease and WHO, which state that BCG discontinuation can be considered in populations with an ARI lower than 0.1% (88, 135).

The results of this study have serious implications for populations in which the risk of congenital immunodeficiencies is elevated. With the availability of bone marrow transplantation, disseminated BCG infection reduces the likelihood of survival among infants with SCID appreciably. The most important factor in improving the prognosis of
an infant with SCID is to diagnose and treat the disease before overwhelming infections occur (136). Unfortunately, inoculation with BCG is usually done within days of birth, substantially increasing the probability of a severe infection and death (71). This model estimates that threshold values for SCID (Figure 9) – above which BCG is not supported given the base values in the model – are lower than the incidence of SCID reported in one North American Aboriginal population, at all levels of risk for tuberculous infection. The occurrence of SCID among Aboriginal infants in Canada is discussed below.

In Monte Carlo simulations, BCG did not have a significantly beneficial impact on the health of children if the risk of SCID was 23 per 100,000 births or higher. At that incidence of SCID, the vaccine significantly reduces quality-adjusted life expectancy in cohorts experiencing an ARI of 0.1%. If the ARI is 1% and the incidence of SCID five per 100,000 or more, there is no significant difference in quality-adjusted life expectancy between vaccinated and unvaccinated children. Although outcomes are not significantly reduced by BCG at these levels, the findings can also be interpreted from the opposite perspective: BCG is not significantly increasing the outcomes either.

5.2 Comparison to the epidemiologic situation (old and new)

Decades ago, there was no doubt that BCG had a positive impact on the health of Canadian children. When it was first administered to First Nations infants in the Fort Qu’Appelle Indian Health Unit in Saskatchewan, an incredible 1% of these infants were dying from TB during the first year of life (33). Death rates were reduced by 80% in vaccinated infants (53), during a period in which antitubercular chemotherapy was not
yet available. A retrospective analysis of data from Quebec showed that the rate of tuberculous meningitis deaths was 0.3 per 100,000 vaccinated children between 1949 and 1956, compared to 2.0 per 100,000 unvaccinated children (137). Only six deaths were reported among 2,000,000 vaccinated children.

The epidemiology and treatment of TB have changed substantially since those periods. Table 4 shows that only five cases of meningeal TB, and seven cases of miliary TB, were reported among First Nations children between 1990 and 2000. None of these children died. Case rates may have been higher in the absence of BCG, but the occurrence of eight deaths associated with the vaccine (Table 2) provides rationale for a discussion on the risk/benefit ratio of this intervention. Analyses of skin testing data and infectious TB disease rates indicate that the risk of infection is less than 0.5% in all provincial First Nations populations (37). One study has shown that the ARI is less than 0.1% among First Nations people in British Columbia (8). BCG was discontinued in that population as of June, 2003.

5.3 Quality of life with neurological sequelae following acute tuberculous meningitis

When considering the benefits of BCG in a population, it is important to take into account more than the TB deaths prevented by vaccination. Residual damage resulting from tuberculous meningitis can range from mild effects (e.g. irritability, limited motor impairment) to very severe effects, leaving the patient either unconscious or completely incapable of an independent existence (110). The majority of patients experience moderate sequelae (110), similar to the health state description developed for this study.
One report found that tuberculous meningitis cases in Manitoba were more likely to be young adults and of Aboriginal origin (128). Although all five reported First Nations cases between 1990 and 2000 survived (Table 4), no data on sequelae were available.

This study found that those interviewed accepted more than a 50% risk of immediate death, on average, to avoid a state of permanent neurological sequelae following acute meningeal TB (Table 6). In communities where transmission is poorly controlled (e.g. the ARI is higher than 1%), BCG may still have a role in protecting children against disability. The model predicts that 13 cases of neurological sequelae will occur in a cohort of 100,000 children over 15 years, if the ARI is 1% (Table 8).

5.4 The risk of SCID among Canadian Aboriginal infants

The elevated rate of disseminated BCG infection observed among vaccinated First Nations newborns during the 1996-2000 period may be an indicator of increased risk for immunodeficiencies in this population. This rate (20 per 100,000, 95% C.I. 6.2, 68) is more than 40 times higher than rates observed in European populations (66). Assuming a case fatality rate of 87% (71), it can be predicted that 17.4 per 100,000 infants would die of disseminated BCG infection in a population with this level of risk. In this study, the model estimates that TB-related deaths do not exceed 7.4 (in a cohort of 100,000 children over 15 years), even if the ARI is 1% and no BCG program is in place (Table 8).

Most forms of SCID are inherited as autosomal recessive traits (74). The risk of diseases inherited in this manner is elevated in communities where gene carriers are present, and parental consanguinity is common. Increased incidence of SCID among
Athabaskan-speaking populations in North America has been associated with the founder effect (138). This phenomenon occurs in populations started from a small number of individuals (or “founders”), in which one or more of the founders were carriers of a particular gene. A similar phenomenon could occur in isolated First Nations and Inuit communities in Canada, where TB – and thus, BCG use – is more prevalent (42). It is also possible that the phenotype has appeared in previous generations undetected, and that deaths among infants with SCID during those periods were attributed solely to the onset of serious infections. Interferon-gamma receptor deficiency, another autosomal recessive immunodeficiency disorder, has also been reported in a First Nations infant with disseminated BCG infection (85).

5.5 Alternatives to BCG vaccination

Safer and more effective alternatives to the current BCG vaccine may soon be available. Recombinant DNA technology has allowed for the development of new BCG strains with better immunogenicity (139). Some of these strains have been shown to be safe in mice with SCID (140), and one induced no cutaneous hypersensitivity to tuberculin (141). The latter feature would be valuable in the context of tuberculin skin testing programs implemented among children who have been previously vaccinated. Non-viable subunit vaccines for TB (both protein and DNA), are also in development, although their efficacy in animal models has generally been similar to or less than that of BCG (142).
One alternative intervention already exists in the form of early detection and treatment of tuberculous infection. The provision of isoniazid is highly effective in reducing the risk of disease (143), and protection may last for up to 30 years (144). Treatment of infection is generally well tolerated by children (145), and compliance is usually much higher than in adults (146, 147). Skin testing at age one year may improve the effectiveness of reverse contact tracing, as the infant has surely been infected during the past year. However, the timing of the skin test is important, due to the early median age at presentation for pediatric miliary TB (10.5 months), and the rapid progression of disseminated primary TB in some infected infants (20, 21). Annual skin testing until the age of five years would likely be required in high-risk settings where BCG is discontinued.

Considering the safety issues outlined in this report, the best course of action may be the removal of BCG vaccine combined with improvements in TB programming. This approach was successful in Beijing, where enhanced TB control efforts were implemented following the discontinuation of BCG, and rates of tuberculous meningitis did not increase (148). The occurrence of large outbreaks and an ongoing cycle of TB transmission in many communities continues to put children at risk for TB. The best way to protect these children is to improve TB control programs, such that cases of infectious TB are prevented or treated early on to block transmission. This will allow children to grow up free from tuberculous infection altogether, making the vaccine question an unnecessary debate. The situation has been summarized as follows: "...if the routine infant BCG vaccine program is abandoned in First Nations communities, this must be compensated for by the support of enhanced detection and treatment programs in these
communities. An effective TB prevention and control program requires effective ascertainment of active disease, effective therapy including Directly Observed Therapy, finding and screening contacts of infectious cases and identification and management of latently infected individuals. Resources must be adequate to support these critical initiatives at the community level. Careful determination of where the gaps in services exist must be made and resources must be allocated to fulfill the requirements. Otherwise, there is little doubt that First Nations infants will be at increased risk of disseminated primary TB disease. Not to increase TB prevention and control programs in these communities is to put these infants at risk” (149).

5.6 Limitations of the model

As with any modelling exercise, predictions in this study depend on assumptions. In an effort to make transition probabilities and utilities in the model meaningful to the study population, values and ranges were estimated with data specific to Canadian Aboriginal populations when possible. Protection from BCG, the risk of TB disease following infection, TB case fatality, the risk of neurological sequelae following tuberculous meningitis, and utility values were estimated using data and studies specific to Canadian Aboriginal populations.

The model did not consider scenarios of partial BCG coverage in the population. However, since the ARI was varied in base case, Markov, and sensitivity analyses, the results of this study can be compared to the epidemiology of TB in different First Nations and Inuit populations, and in specific geographic areas. The risk of TB among
Aboriginal peoples varies by province, and even within provinces (37, 40). If policy
decisions were based on the results shown in Figure 9, BCG coverage in the Aboriginal
population may be targeted to certain areas, covering neither 0% nor 100% of the overall
population. Hypothetically, uptake may also depend on regional risks of SCID among
Aboriginal newborns.

Secondary effects of BCG vaccination due to reduced transmission were not
included in the model. Although BCG has been associated with a reduced risk of
disseminated TB disease (26), there is no evidence that BCG has reduced the risk of TB
infection in any population (150). In the absence of such evidence, estimating the
theoretical herd immunity effects of BCG is of little utility (63). For these reasons, the
Markov modeling approach was considered suitable for this study, and transmission was
not included in the model. For infectious diseases such as measles, more complex
methods of modeling are necessary to simulate the substantial secondary benefits of
immunization strategies (151, 152). The possible use of a new and better TB vaccine as a
control agent has been examined using advanced modeling techniques (153).

The risk of BCG infection in HIV-positive children was not considered in the
model. Due to the new FNIHB policy requiring that the HIV status of mothers be known
prior to giving BCG, a measure of HIV vertical transmission to newborns does not equate
to an appreciable level of risk for disseminated BCG infection in areas where the vaccine
is used. This means that BCG could only be given to an HIV-infected infant due to a
serious error by health care providers, something which is difficult to quantify. Of
greater concern is the threat of inherited immunodeficiencies such as SCID, for which the
situation is very different. Unlike HIV, there is no reliable screening test for SCID at
birth, and family history is currently the only method of assessing risk. The death of three related infants in Manitoba due to disseminated BCG infection, including one this year (Table 2), suggests that a positive family history for SCID does not affect the decision to give BCG in the field.

There were limitations in the methods used to elicit health state utility values. The study did not seek a random sample of the general population for interviews, and it is possible that factors such as ethnicity could have affected utility scores if sample sizes were larger. Despite this, mean values for all groups considered in Table 6 fall within the 95% confidence limits for the overall mean (0.37-0.49), the range used for variability and uncertainty analyses. Analyses showed that interview group, age, sex, and other factors did not affect the results. It has been observed in other studies that preference values are generally quite stable across different groups, whether male or female, young or old, etc. (154).

Adverse events associated with BCG other than disseminated infection, such as adenitis (50) and osteomyelitis (66), were not included in the model. Rouillon and Waaler (103) found that these reactions did not contraindicate the risk of BCG under any epidemiologic conditions, although they made the same observation for the risk of disseminated BCG infection. This model has considered disseminated BCG infection due to its higher frequency among Canadian Aboriginal peoples, and its ominous tendency to cause death in young infants. The effects of treatment side effects on quality of life were also neglected in the model, and utility values for acute TB disease states were based solely on hospitalization data.
Finally, the model did not consider a lifetime horizon, which has been recommended for decision analyses (117). This study considered a time horizon of 15 years, which is consistent with other modelling studies on BCG (103, 104), and evidence for the duration of protection induced by the vaccine (27, 55). Arvanitakis et al. reported that tuberculous meningitis tends to occur among young Aboriginal adults, despite prior vaccination with BCG (128). Since the objective of neonatal BCG vaccination in Canada is to prevent death and disability in children (134), a 15-year time horizon was considered suitable for this study.

5.7 Strengths of the model

This model considered the effectiveness of BCG demonstrated in studies specific to Canadian First Nations populations (53, 90, 91), and meta analyses (26, 27). Model predictions of age-specific meningeal and miliary TB rates are similar to published analyses of surveillance data (18, 19). The natural history of TB in the model is consistent with recent modelling studies, including states of primary tuberculous infection, latent infection and reinfection (6,7). Utility values in the model were estimated using recognized methods (108, 131). As described above, the majority of probability estimates and utility values were based on data specific to Canadian Aboriginal populations. Since BCG is given in this population, the results of the model can be used to guide relevant recommendations and policy decisions.

This is the first model to date which considers the impact of SCID incidence on the decision to give BCG, which may be an important criterion for BCG vaccination
policies in populations at increased risk. Uncertainty and variability analyses showed that the model was robust, and the results of sensitivity analyses show that threshold values for SCID are stable when other parameters in the model are varied across plausible ranges.
6 CONCLUSIONS

The epidemiologic situation has changed substantially since BCG programs were first implemented in Canadian Aboriginal communities. TB mortality rates are a small fraction of what they were during the prechemotherapy era, and far fewer children are exposed to tuberculous infection as they grow up. Despite this, First Nations and Inuit peoples in Canada continue to experience a disproportionate burden of TB, and children in many communities are still at risk. The occurrence of deaths associated with BCG provides rationale for a discussion on the risks of continued BCG use, and a review of BCG policy in Canada. The results of this model were highly sensitive to the risks of SCID and disseminated BCG infection among vaccinated infants. The best course of action may be an increased investment in alternative TB prevention and control measures, to lessen our reliance on BCG vaccine. Future research should focus on the relative effectiveness of such measures, and the development of better TB vaccines. It would also be beneficial to determine the true incidence of SCID among Canadian Aboriginal people, so that comparisons can be made to the thresholds estimated in this study.
REFERENCES


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## Appendix 1. Microsoft Excel computer tool for interviews

<table>
<thead>
<tr>
<th>Chance Board</th>
<th>Health State Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choice &quot;A&quot;</strong></td>
<td><strong>Choice &quot;A&quot;</strong></td>
</tr>
<tr>
<td>Perfect health</td>
<td>If chosen, you will have two possible results:</td>
</tr>
<tr>
<td>100 %</td>
<td>1 Perfect health; or</td>
</tr>
<tr>
<td>Death</td>
<td>2 Death</td>
</tr>
<tr>
<td>0 %</td>
<td>For every 100 patients who choose &quot;A&quot;:</td>
</tr>
<tr>
<td></td>
<td>100 will become perfectly healthy; and</td>
</tr>
<tr>
<td></td>
<td>0 will die during treatment</td>
</tr>
</tbody>
</table>

### Choice "B"

- **Health state** 100 %

### Choice "B"

- One side of your entire body is partially paralyzed, and your limbs make involuntary movements.
- Parts of your body feel “frozen,” causing some discomfort.
- You make impulsive, sometimes unwise decisions, and lack the functional skills needed for many forms of employment.
- You find it difficult to communicate effectively with others, and need help taking care of yourself at home.
Appendix 2. Health state descriptions

PERFECT HEALTH

VISION: You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

HEARING: You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.

SPEECH: You are able to be understood completely when speaking with strangers or friends.

AMBULATION: You are able to walk around the neighbourhood without difficulty, and without walking equipment.

DEXTERITY: You have full use of two hands and ten fingers.

EMOTION: You are happy and interested in life.

COGNITION: You are able to remember most things, think clearly, and solve day to day problems.

PAIN: You are free of pain and discomfort.
CONDITION “X”

One side of your entire body is partially paralyzed, and your limbs make involuntary movements. Parts of your body feel “frozen,” causing some discomfort. You make impulsive, sometimes unwise decisions, and lack the functional skills needed for many forms of employment. You find it difficult to communicate effectively with others, and need help taking care of yourself at home.

VISION: You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

HEARING: You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.

SPEECH: You are able to be understood partially when speaking with strangers or people who know you well.

AMBULATION: You are able to walk only short distances with walking equipment, and you require a wheelchair to get around the neighbourhood.

DEXTERITY: You are limited in the use of your hands and fingers, and will require the help of another for some tasks.

EMOTION: You feel somewhat unhappy.

COGNITION: You are somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems.

PAIN: You have moderate pain that prevents a few activities.
Appendix 3. Ottawa Hospital Research Ethics Board letter of approval

Wednesday, July 09, 2003

Dr. Graham Nichol
Ottawa Hospital - Civic Campus
Ottawa Health Research Institute
Clinical Epidemiology Unit

Dear Dr. Nichol,

Re: Protocol # 2003312-01H Elicitation of Utilities for Health States Associated with two Chronic Infectious Diseases

Protocol approval valid until - Tuesday, September 09, 2003

I am pleased to inform you that your study (listed above) was given expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and approved for two months to recruit English-speaking patients. Upon receipt and review of the French Informed Consent and Information Sheet, approval may be extended to July 8, 2004 (one year from the date of the initial approval) and the recruitment of French-speaking patients may begin. No changes, amendments or addenda may be made in the protocol without the OHREB review and approval.

The validation dated should be indicated on the bottom of all consent forms and information sheets (see copy attached). Approximately two months prior to the expiration date listed above, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. You must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board
Appendix 4. Respondent consent form for utility collection

**Title of Study**: Elicitation of utilities for health states associated with two chronic infectious diseases.

**Investigator Name**: Dr. Graham Nichol, Tel:

**Purpose of the Study**: You are being asked to participate in a research study to determine public preferences for policies on vaccination. The objective is to assess how people feel about quality of life experienced by persons with two health conditions caused by infections.

**Description of the Study**: The study consists of an interview. The investigator will ask a series of questions, and assist you with a computer tool developed in Microsoft Excel. Visuals aids and the computer tool will be used to describe different health states.

**Study Procedures**: If you choose to participate in this study, you will be asked to sign a copy of this informed consent. The investigator will then ask some questions, such as your age, and highest level of education attained. You will then be asked to read three descriptions, describing a state of perfect health, and a person's life with two chronic conditions. With the help of the interviewer you will then complete an exercise in Microsoft Excel asking your preferences for different health states. The interview will be carried out in English.

**Risks/Benefits**: The study consists of an interview only. There will be no potential risks to participating in the study. Your participation will help us to understand how people feel about quality of life with different health conditions.

**Study Participation**: Your participation in this study is entirely voluntary.

**Withdrawal from Study**: If you choose to participate you are free to withdraw from this study at any time.

**Confidentiality**: All results of this study will be kept confidential. Your name or any material identifying you as a study participant will not be released. You will not be identifiable in any publication, report or presentation resulting from this study. No records bearing your name will leave the Ottawa Hospital.

**Information**: If you have any questions regarding this study, you may contact Dr. Graham Nichol at

93
AGREEMENT TO PARTICIPATE IN STUDY/SIGNATURE

My signature below indicates that I have read all of the above information about this research study. The content and meaning of this information have been explained and are understood. I have had the opportunity to ask questions. I will be given a copy of this informed consent.

Participant Signature ___________________________ Date __________

Participant Name (please print) ______________________________________

I have explained the above to the participant on the date stated on this Informed Consent.

Investigator/Delegate Signature ___________________________ Date __________

Investigator/Delegate Name ______________________________________

(Valid until September 9, 2003)
Appendix 5. Letter of permission for interviews at the Akwesasne Department of Social Development and Health

MOHAWK COUNCIL OF AKWESASNE

July 7, 2003

Michael Clark  
Primary Health Care and Public Health Div.  
First Nations & Inuit Health Branch

RE: SURVEY APPROVAL

Dear Mr. Clark:

In regards to your study, Elicitation of Utilities for Health States Associated with Two Chronic Infectious Diseases, I give my approval of conducting a survey amongst my Department of Health staff, provided the survey results are shared with our department and community.

Thank you for your valued assistance.

Sincerely,

Brenda Lafrance  
Director  
Department of Health, Akwesasne