“To BCG or not to BCG, that is the question!”. The challenge of BCG vaccination: Why can't we get it right?

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Although the Bacille Calmette-Guerin (BCG) vaccine has been in use since 1921 and has been given to more people in the world than any other vaccine, controversy continues around its use and is even escalating. Currently in Canada, the BCG vaccine is given routinely to newborns in First Nations communities. This practice is under active review because of concerns that the vaccine's safety may outweigh the efficacy of the vaccine. The benefits of BCG have been hotly debated for many years and consensus has been hard to come by. After much debate and confusion, and seemingly endless review articles and meta-analyses, the prize of international consensus is still elusive. The thoroughness of the recent review literature makes another review article redundant. The purpose of this discussion is to familiarize the Canadian paediatric community with the issues so that its members can at least understand the language of the debate, if not actively participate and come to some conclusions!

There are a few basic questions to be addressed:

What is the BCG vaccine and why is it used in Canada?

BCG is an attenuated live strain of *Mycobacterium bovis*. When inoculated it causes a mild, often symptomatic, systemic infection that may then confer cross immunity to *M. tuberculosis*, a part of the same mycobacterial complex. The vaccine was studied initially during the 1930s, and widely administered before World War II. It was studied extensively in the 1950s in both North America and Europe, and these studies gave rise to conflicting results. Thus, the initial recommendations from various national organizations conflicted, and a historical precedent was set for international disagreement.

In North America its use is currently limited to select high risk populations (1). The vaccine may be considered in select situations where exposure to tuberculosis (TB) infection cannot be readily controlled with antituberculous chemotherapy, particularly where multidrug resistance is documented. The recipients in this situation may include household contacts as well as laboratory personnel and travelers (2). In Canada, newborn infants in First Nations communities have been routinely immunized since 1948. A review of the rationale for this practice follows.

TB epidemiology in Canada is closely monitored by the Canadian Tuberculosis Reporting System. The highest number of cases nationally are reported in foreign-born individuals and these cases are mostly reported in adults (3). However, the highest number of cases in children, cases of primary TB and the highest population based rate of infection are found in the Canadian-born Aboriginal population (3,4). The notification rate of active TB cases in this population in 1999 (the last year for which rates are published) was 61.5/100,000, which is not significantly different from the rate of 74.8/100,000 reported from 1992. The rate of infection in this population reaches seven to 10 times the rate of infection in the non-Aboriginal Canadian-born population. The reported rate of infection in Canadian-born Aboriginal children 15 years and younger decreased over the 10 years (1990 to 1999) from 139 to 57/100,000. The reported rates of active TB in Canadian-born Aboriginal children are highest in Saskatchewan where the reported rate decreased from 626 to 241/100,000 over the same time period (4).

Current control measures such as case finding and Directly Observed Therapy have succeeded in controlling

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the rate of infection but not reducing it as quickly as had been hoped when the national TB Elimination Strategy was implemented in 1992 (4).

While compliance with therapy of active TB is good in more than 90% in most communities, compliance with chemoprophylaxis for latent infection is much poorer. It is estimated that from western Ontario to British Columbia, 20% to 60% of the adult Aboriginal population is latently infected with TB and this provides a large reservoir for potential newly infectious cases (4).

Therefore, young infants in Aboriginal communities continue to be at risk of exposure to TB, and when primary infection occurs in young children the risk of dissemination with miliary disease and meningitis is significant. Tuberculous meningitis will develop in 1% to 2% of children infected with TB (5), and this usually develops soon after the primary infection. The younger the child the higher the risk of dissemination. Because TB meningitis and dissemination occur soon after the primary infection, and many First Nations communities are geographically isolated and children may have a delay in obtaining medical attention, the risk of serious sequelae or mortality for infected children remains high.

The high rate of TB infection in the Aboriginal population and the high risk of serious disease in young children after primary infection have been the rationale for Health Canada to recommend administration of BCG vaccine to all newborn infants who are members of First Nations communities across the country. This policy is now being reconsidered in light of the following questions.

Does the BCG vaccine work?

This is the proverbial \$64,000 question. The reported efficacy of BCG vaccine against pulmonary TB has ranged from 0% to over 80% (6). Three important meta-analyses were published in the mid-1990s (7-9), one from Europe and two from the United States by the same lead author — one focusing on infants (8). All conclude that BCG is effective for the prevention of TB with a protective effect of at least 50% overall. The studies also conclude there is greater effectiveness for disseminated disease and meningitis with a calculated protective effect as high as 86%. There was, however, wide variability within the trials studied and disagreement as to which studies should be included and debate as to whether conclusions could be drawn from studies with great ranges of heterogeneity between data sets (6). Two subsequent studies published from Malawi showed no protective effect from BCG for TB (10,11). More cases of pulmonary TB were observed in the BCG vaccine group. Although this difference was not statistically significant, it may have reflected a trend to worse disease in an human immunodeficiency virus (HIV)-infected population, raising the concern for risk of disease from BCG in the immunocompromised.

Why is there such controversy? First of all, TB is not a homogeneous disease. Combining reactivation pulmonary disease with primary disseminated disease in efficacy analy-

sis is misleading. The differences in the reported efficacy of the vaccine may be a result of comparing efficacy in two very different disease processes. The protective effect for miliary disease and meningitis was much more homogeneous and was calculated to be 86% in randomized controlled trials (RCTs) and 75% in case-control studies. The current Canadian practice of BCG administration to high risk newborns is supported by several RCTs (including one Canadian study) in which the vaccine was administered to newborn infants before environmental exposure to mycobacteria could have occurred (12-16). These original studies showed an overall efficacy of 73% (range 59% to 80%) for disease and 87% for death. However, when data from all well-designed trials in infants were combined, the efficacy for protection from all TB is somewhat lower at "over 50%" with protective effects for the RCTs at 0.74 and the case-control studies at 0.52 (8). The conclusions from two Canadian case control studies support this range of effectiveness of between 50% and 60% (17,18). Interestingly the Alberta study did not seem to support the selective protection for miliary disease as all three cases of miliary TB reported in the study had records of having been given BCG (17).

The second reason for the efficacy controversy is the clear variability in protection between different geographic locations. Many investigators have observed a geographic gradient in effectiveness (lower in the warmer equatorial regions and higher in northern regions like Canada). There are many hypotheses for this variability, including differences in TB virulence, genetic susceptibility of the population and BCG potency. Differences in genomic composition as a result of the ongoing evolution of the original BCG strain have been well described (19) and may contribute to the observed differences in immunogenicity. However, the most likely explanation for this phenomenon is the difference in exposure to environmental mycobacteria. The greater the endemic exposure to environmental mycobacteria, the lower the efficacy of the vaccine in the population. The population could be partially immune from the environmental exposure and the resulting cross resistance would result in a diminished observed effect for the exogenous BCG strain, or conversely, the population may not react to BCG because of pre-existing immunity that would prevent the BCG strain from establishing active replication and render it ineffective (6,12). In the Canadian context this could encourage interpretation of efficacy of BCG vaccine to be better than the average. (One important advantage of our northern location!).

What does all this mean? There is clearly real variability from study to study that is not just from chance or bad science. The overall trends are that newborns are better protected and primary disease, miliary disease and meningitis are better prevented. For all these conditions, BCG may be more effective in a northern climate.

Does BCG cause harm?

The debate about this vaccine in Canada has accelerated as a result of concerns about adverse events. Although BCG is

known frequently to cause local reactions consistent with primary infection with an attenuated strain (ie, a small localized ulcer and possible regional lymphadenopathy), more severe reactions are thought to be rare. Deep ulcers, prolonged drainage, lymphadenitis (1%), abscess (2%) (20), osteitis (0.04%) (21) and rarely disseminated infection have been reported (22). The age of the recipient and the dose of vaccine affect the incidence of local complications. Disseminated disease is thought to be rare, in the order of 1/1,000,000 doses and directly related to immune dysfunction (20). The major concern world-wide with the risk of disseminated infection has been related to the risk of HIV-related immunocompromise in the recipient.

The Canadian Paediatric Society's Immunization Monitoring Program ACTive (IMPACT) network, which actively surveys for vaccine adverse events in hospitalized children (covering 90% of tertiary care paediatric beds in the country), has included BCG adverse events in its data collection. From 1993 to 2001, 20 adverse events were reported. Six of these were disseminated disease and five were in First Nations children (the sixth one was vaccinated as an infant outside Canada). All these cases were assessed by the Advisory Committee on Causality Assessment of Health Canada and were assessed as being caused by BCG (personal communication, Shelley Deeks). One of these children was HIV-infected and the other four had congenital immunodeficiencies, which presented for the first time as disseminated BCG infection. All these children died as a result of their underlying immunodeficiency. This rate of disseminated infection is much higher than what would be predicted with a 1/1,000,000 incidence and likely indicates a higher rate of underlying congenital immunodeficiency in this population and graphically indicates an unanticipated serious risk in this population of BCG recipients (23).

Another concern with the administration of BCG is its effect on the tuberculin skin test. Because administration of BCG induces a positive skin test of variable size in a large proportion of vaccinated individuals, this reaction will make the interpretation of skin test results in contact tracing more difficult and, thus, damage a valuable tool in the control of TB transmission in the community.

What are the alternatives now?

A significant risk of disseminated BCG has been described in infants in First Nations communities. The place of BCG vaccination in TB control programs in Canada is therefore being carefully reassessed. While BCG continues to be administered in this population, a careful review and identification of underlying risks for immunodeficiency should also be performed. This should include a careful family history for immunodeficiency and prenatal HIV screening. If BCG is no longer to be given routinely to newborns in First Nations communities, then possible consequences must be anticipated. The rates of miliary TB and meningitis in Canadian infants are very low at present; however, given the apparent efficacy of BCG to prevent this disease, it is

likely that the incidence of this disease will increase if ongoing exposure of young infants continues. Sweden moved from the mass vaccination of newborns with BCG to a selective vaccination program for high risk groups. This strategy met with some success, measured at 82% effectiveness (24). This was accompanied by a higher rate of atypical mycobacterial infection in the non-BCG-vaccinated population (25). In Canada the high risk population is already being vaccinated, but higher selectivity may be required given the identified risk of the vaccine; possibly limiting newborn BCG use to communities with active cases until the outbreak can be brought under control.

Alternative vaccines to BCG are on the horizon and it is hoped that they will have better efficacy, be more standardized and have fewer side effects, especially in the immunocompromised, including the HIV-infected population world-wide, which is at high risk of TB coinfection. Candidate vaccines include attenuated whole-cell live, whole-cell inactivated, subunit, DNA and prime-boost vaccines. Human trials are underway for many of these but long term efficacy results will be required (12).

In the meantime, 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.

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