The Effect of Neonatal Bacille Calmette-Guérin Vaccination on Purified Protein Derivative Skin Test Results in Canadian Aboriginal Children*

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Background: **The effect that neonatal bacille Calmette-Guérin (BCG) vaccination has on tuberculin skin test (TST) results is not well evaluated in preschool children.**

Methods: **This was a retrospective cohort study of TST results in aboriginal children in Saskatchewan reserve communities. Records from the centralized provincial tuberculosis program were searched for aboriginal children aged 0 to 4 years during the time period 1991 to 1999. Only the first TST result reported as part of infant and preschool screening programs was considered. Children with active tuberculosis and those evaluated as part of a contact-tracing program were excluded. The BCG-vaccinated and unvaccinated groups were compared using wheal size cut points of 5 mm, 10 mm, and 15 mm.**

Results: **Data from 1,086 children with neonatal BCG vaccination and 1,867 unvaccinated children were analyzed. The rate of TST reactions was higher in vaccinated children at all ages, using a cut point of 5 mm. The rate of TST reactions was no different in vaccinated children ≥ 1 year old when using a cut point of 15 mm. When using a cut point of 10 mm, the rate of TST reactions was higher at age 1 year but not different at age 4 years in the vaccinated children.**

Conclusion: **The rate of TST reactions in preschool aboriginal children living on a reserve who have received neonatal BCG vaccination is affected by the cut point and age. The BCG vaccination status and age should therefore be considered when interpreting TST reactivity in the clinical assessment of aboriginal children participating in a tuberculosis control program.**

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Key words: bacille Calmette-Guérin; tuberculosis; tuberculosis testing; vaccination

Abbreviations: BCG = bacille Calmette-Guérin; TST = tuberculin skin test; TU = tuberculin unit

In Saskatchewan, the highest rate of *Mycobacterium tuberculosis* is among the aboriginal population. To reduce the incidence of active tuberculosis and particularly serious complications such as tuberculosis meningitis and disseminated tuberculosis, neonatal bacille Calmette-Guérin (BCG) vaccination (0.05 mL via intracutaneous injection) is offered to all aboriginal children living in First Nations communities (reserves), in keeping with Health Canada recommendations.[1] BCG vaccination is offered within days of birth to all eligible children. Unfortunately, many do not receive it, and the vaccination coverage rate is only 50%.

The tuberculin skin test (TST) is the standard method of detecting *M tuberculosis* infection.[2,3] It is an important tool in the assessment of persons at risk for tuberculosis, especially children, and it is recommended for aboriginal children living in First Nations communities at age 1 to 2 years and again at

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school entry. TSTs are administered in Saskatchewan as outlined in the Canadian Tuberculosis Standards.[2] A dose of 0.1 mL (5 tuberculin units [TU]) of purified protein derivative is injected intradermally on the volar aspect of the forearm, and the reaction is read 48 to 72 h later. BCG vaccination can influence the size of the TST reaction,[4–11] and no reliable method exists to distinguish reactions caused by BCG from those caused by *M tuberculosis*. Interferon-γ release assays have been recently reported to have superior specificity to the TST for detecting *M tuberculosis* infection in BCG-vaccinated individuals.[12] However, data in young children are limited, and these tests have not yet received universal acceptance.[12] Furthermore, they are not available in Saskatchewan. Variables that have been shown to affect the skin test reaction include the age at vaccination,[4,6,12,13] the interval between the vaccination and skin test,[14] the frequency of vaccination,[8,15–17] frequency of skin testing,[3,8,15,18,19] and the type of TST used.[20,21] The effect of BCG on the TST reaction wanes with time,[4,6,13,14,22–25] but reports[4–6,9,10,22,24–26] have varied as to how long this takes. While there is agreement that the influence of neonatal BCG is not as long lasting as that of BCG administered after the first year of life,[4,6] reports have varied as to how long this effect does last.[4–6,9,10,22,24–26] It is generally accepted that neonatal BCG will have an effect on the TST reaction within a few weeks, and that this effect will last for at least the first year of life before waning. By 10 years after vaccination, neonatal BCG seems to have no effect on the TST result when ≥ 10 mm is used as the cut point.[6] However, it is less certain what effect neonatal BCG has on TST reactions in the first 5 years.

American and Canadian thoracic societies recommend 10 mm as the diagnostic cut point for *M tuberculosis* in most situations, but 5 mm is the recommended cut point in conditions of greater risk.[2] Furthermore, the American Thoracic Society suggests a cut point of 15 mm be used for patients with no risk factors for *M tuberculosis*.[3] We assessed how the association between neonatal-BCG and TST reactivity was influenced by these three different cut points and whether this was affected by tuberculosis exposure.

The Saskatchewan Tuberculosis Program maintains a centralized database that includes information on BCG provision to newborns, TST results for infants and children, as well as demographic data. This database also includes cases of infectious *M tuberculosis* (smear positive for adults). We were therefore able to compare the TST reactions in children who were similar for ethnic, socioeconomic, and geographic factors, as well as background risk of tuberculosis exposure. By comparing vaccinated with unvaccinated children, we could thereby isolate the effect of BCG on the TST reaction.

Materials and Methods

This research was a quality control assessment of a provincial program. As such, institutional review board approval was not required. Data were collected for all aboriginal children living on a reserve aged 5 weeks to 4 years who were born between 1991 and 1999, and who had at least one TST record. Four years of age was defined as up to but not including the fifth birthday. Patients with a clinical or bacteriologic diagnosis of tuberculosis and children whose skin tests were part of a contact-tracing program were excluded. To eliminate any possible TST-boosting effect,[3,6,8,15,17,19,20,22] only the first skin test for each child was considered. Children were grouped according to whether or not they had received neonatal BCG vaccination. The groups were then compared according to the rate of TST reactions at 1-year intervals using cut points of 5 mm, 10 mm, and 15 mm. To illustrate the effect of BCG, we subtracted the percentage of unvaccinated children with a TST reaction from that of BCG-vaccinated children. We did this for each year of the cohort.

Statistical Analysis

The mean annual population of aboriginal children living on Saskatchewan reserves aged 0 to 4 years and mean annual number of BCG vaccinations were calculated from the Saskatchewan tuberculosis control database. Frequencies of children who had a TST result at the cut points of 5 mm, 10 mm, and 15 mm were also identified. A series of χ^2 tests were performed to compare the BCG vaccination group with the unvaccinated group, using TST cut points of 5 mm, 10 mm, and 15 mm. Statistical significance was defined at $p < 0.05$. Statistical analysis was completed using statistical software (SPSS version 11.0; SPSS; Chicago, IL).

Results

For aboriginal children living on a reserve, the mean annual 0- to 4-year age population from 1991 to 1999 was 5,057. The mean annual number of neonatal BCG vaccinations from 1991 to 1999 in this group was 693. Mean annual rates of infectious tuberculosis (adult, "smear positive") were 23/100,000 from 1991 to 1995 and 22/100,000 from 1995 to 1999. One thousand ninety children were excluded, one third because they had tuberculosis disease and two thirds because they were contacts of a known case. The male to female ratio of this group was approximately 50%. The TST responses in this excluded group were as follows: 573 reactions < 5 mm; 123 reactions 5 to 9 mm; 249 reactions 10 to 14 mm; and 145 reactions ≥ 15 mm. Of the study group, a total of 1,086 aboriginal children received neonatal BCG and 1,867 children went unvaccinated. Both groups had approximately equal number of male and female children. There were 2,953 children aged 5 weeks to 4 years who had a TST record between 1991 and 1999.