A Case-Control Study to Evaluate the Effectiveness of Mass Neonatal BCG Vaccination among Canadian Indians

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Abstract: This paper reports a case-control study to assess the protective effect of BCG (bacille Calmette-Guérin) vaccination among Indian infants in Manitoba, Canada. A record of past BCG vaccination was found in 49 per cent of the tuberculosis cases, compared to 77 per cent of the controls, yielding a relative risk of 0.30. Stratified analysis, controlling for age, increased the relative risk to 0.39 (95% confidence interval 0.22 – 0.69). The preventive fraction was 44 per cent. Non-differential misclassification of exposure status could have occurred; if this was adjusted for, the relative risk would be reduced. If only bacteriologically confirmed cases were analyzed, the age-adjusted relative risk was 0.27. The protective effect of BCG vaccination in the newborn among Manitoba Indians is therefore at least 60 per cent. The implications for health policy in this population are further discussed. (*Am J Public Health* 1986; 76:783–786.)

Introduction

BCG (bacille Calmette-Guérin) vaccination to control tuberculosis is widely practiced around the world, but conflicting results from several large-scale trials have cast doubt on its effectiveness.[1–3] Despite the disappointing results of the latest trial in Madras, India,[4] expert committees of the World Health Organization continue to recommend the mass use of BCG vaccination in developing countries, and stress the need for further research.[5–7]

In Canada, Indian and Inuit (Eskimo) newborns are one of the few high-risk groups which still receive BCG routinely. This policy of the federal Medical Services has been in force at least since the mid–1960s. The use of BCG on a mass scale in this population is still recommended by the most recent edition of the Canadian Tuberculosis Standards published by the national lung association.[8] In Manitoba, freeze-dried BCG manufactured by Connaught Laboratories is used. The dose for infants is 0.05 mg (half the adult dose) administered intradermally.

Raj Narain, former Director of the Madras Tuberculosis Prevention Trial, advocated the conduct of a randomized controlled trial of BCG vaccination among Canadian Indians and Inuit in 1982.[9] An alternative, suggested by Smith, was a case-control study.[10]

In this paper, we report a case-control study to determine the effectiveness of BCG vaccination of newborns in preventing the development of tuberculosis among Indians in Manitoba.

Methods

Selection of Cases

Cases of new active tuberculosis diagnosed between 1979 and 1983 among Registered Indians living on Indian Reserves were obtained from the Manitoba Tuberculosis Registry in Winnipeg. Notification of tuberculosis is required by law; treatment services for this disease, while no longer sanatorium-based, are centralized in one facility in this province. The Provincial Tuberculosis Control Services contracts with the federal Medical Services Branch to provide diagnostic, treatment, and follow-up services for all Indian tuberculosis patients. There is thus a high degree of completeness in the ascertainment of cases for the population studied.

Cases were restricted to those born on or after January 1, 1965—those most likely to have benefited from the mass BCG program and most likely to have adequate records. Only childhood cases (under the age of 15 at the time of diagnosis) were considered. These cases from a population-based registry were therefore all incident, rather than prevalent, cases.

No attempt was made to validate the diagnostic accuracy of the cases in the Registry, but separate analyses were made for all registered cases, and for cases which were bacteriologically confirmed.

A total of 71 cases were selected. All records and immunization cards were reviewed and abstracts prepared by the principal investigator during visits to all facilities. Fifty cases were classified as primary, 11 pulmonary, five pleurisy, two miliary, two lymph nodes, and one disseminated. No meningitis case occurred during the period studied.

Selection of Controls

Controls were randomly selected from the general Registered Indian population in the same communities which contributed tuberculosis cases, with the same age restriction. Matching on an individual basis was not performed; the problem of potential confounding was handled by stratified analysis. Three times as many controls as cases were selected.

The controls were all living and never had active tuberculosis up to the time of the investigator's site visit. As they were selected from a listing of the communities' residents, they were representative of the general population at risk.

All records and immunization cards were reviewed and abstracts prepared by the principal investigator during visits to the health facilities.

The ages of individuals when vaccinated were not consistently recorded. However, the official policy had always been to give BCG at birth prior to discharge from hospital. Infants who were missed at birth (for a variety of reasons such as lack of cooperation or enthusiasm of some local hospitals) were "caught up" by public health nurses during regular well-child clinics.

Statistical Analysis

The measure of association between past BCG vaccination and development of new active tuberculosis is the odds ratio which provides an estimate of the relative risk (R). For

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TABLE 1—Comparison of Cases and Controls with regard to Age, Sex, and Past Isoniazid Use

Variables		Cases		Controls	
		No.	%	No.	%
Sex	Male	40	56.3	103	48.4
	Female	31	43.7	110	51.6
Year of Birth	1965–69	19	26.8	34	16.0
	1970–74	33	46.5	59	27.7
	1965–74	52	73.3	93	43.7
	1975–79	13	18.3	69	32.4
	1980–83	6	8.5	51	23.9
	1975–83	19	26.8	120	56.3
Past Isoniazid Use	Yes	4	5.6	7	3.3
	No	67	94.4	206	96.7

BCG to be effective in preventing tuberculosis, R should be less than 1. The protective effect of BCG is then 100 (1–R) per cent.

Disease status and exposure status were dichotomized into "case" or "control", and "BCG" or "non-BCG", respectively. Stratified analyses of a series of 2×2 contingency tables were performed according to the methods described by Mantel and Haenszel[11] and Miettinen[12] which gave summary estimates of relative risks across all strata as well as their 95 per cent confidence intervals. Computations were facilitated by the use of the HP-41CV programmable calculator and the published programs by Rothman and Boice.[13]

Variables to be controlled for include age (year of birth), sex, locality ("northern, remote" vs "southern, road-accessible"), and history of past isoniazid prophylaxis. Past use of isoniazid is not strictly a potential confounder, since it is not associated with the exposure in question, although it is expected to affect the incidence of disease. Past prophylaxis may have a possible interactive effect with vaccination in that a person who has received both BCG and isoniazid may have a much reduced chance of developing tuberculosis. On the other hand, a person who receives isoniazid prophylaxis is usually at higher risk for the disease because of close contact with an active case.

Results

Overall, 49.3 per cent of cases had a record of past BCG vaccination, compared to 76.5 per cent of controls. The crude (unadjusted) relative risk was 0.30 (95% confidence interval 0.17 to 0.52).

Table 1 compares cases and controls with regard to age distribution, sex, and past usage of isoniazid. Older cases and controls tend to have a lower vaccination coverage than those born more recently. Since the sampling was stratified by community, the distribution of locality types was identical in both cases and controls.

Table 2 indicates that age adjustment alone increased the overall relative risk from 0.30 to 0.39 (95% confidence interval 0.22 to 0.69). Whether two strata (year of birth 1965–74, and 1975–83) or four strata (1965–69, 1970–74, 1975–79, and 1980–83) were used in the calculation had little effect on the adjusted relative risk. Subsequent analyses will therefore only adjust for year of birth based on two strata.

To investigate the possibility that some of the "cases" recorded in the Tuberculosis Registry were not in fact true cases, the analysis was repeated using only bacteriologically confirmed cases. These 37 cases had some type of body specimen (sputum, gastric aspirate, cerebrospinal fluid, urine, lymph node discharge, etc.,) positive on either smear or culture. The age-adjusted relative risk was now 0.27 (95% confidence interval 0.13 to 0.56) (Table 3).

Misclassification of exposure status was also a possibility since the study depended on the quality of existing health service records. Over the years, records were handled by numerous health workers. If a person did not receive BCG, it seems unlikely that it would be recorded as having been given; more likely, a person may have received BCG without a record having been made. It is reasonable to assume that any misclassification that did occur would be of the "non-differential" type, i.e., cases and controls were equally likely to have their vaccination status recorded incorrectly to the same degree. Under this set of assumptions, correcting for

TABLE 2—Stratified Analyses of the Association between BCG Vaccination and Tuberculosis

Variable Adjusted	Strata	Cases		Controls			
		No.	% BCG	No.	% BCG	RR^{mh}	95% Confidence Interval
nil	—	71	49.3	213	76.5	0.30	0.17–0.52
Year of Birth	1965–69	19	47.4	34	58.8		
	1970–74	33	42.4	59	67.8		
	1975–79	13	61.5	69	82.6		
	1980–83	6	66.7	51	90.2	0.40	0.22–0.70
	1965–74	52	44.2	93	64.5		
	1975–83	19	63.2	120	85.8	0.39	0.22–0.69
Sex	Male	40	55.0	103	73.8		
	Female	31	41.9	110	79.1	0.30	0.18–0.52
Past Isoniazid Use	Yes	4	25.0	7	85.7		
	No	67	50.8	206	76.2	0.30	0.17–0.52
Locale	North	31	74.2	93	88.2		
	South	40	30.0	120	67.5	0.26	0.14–0.46
	21 individual communities					0.23	0.12–0.43
Year of Birth and Sex	(4 strata)					0.39	0.22–0.70
Year of Birth and Location	(4 strata)					0.35	0.19–0.66
Sex and Location	(4 strata)					0.26	0.15–0.47
Year of Birth and Sex and Isoniazid Use	(8 strata)					0.40	0.23–0.70

Notes: RR_{mh} = Mantel-Haenszel summary estimate of relative risk.

TABLE 3—Selected Analyses Using Only Bacteriologically Confirmed Cases

Variable Adjusted	Strata	Cases		Controls			
		No.	% BCG	No.	% BCG	RR_{mh}	95% Confidence Interval
nil	—	37	40.5	213	76.5	0.21	0.11–0.42
Year of Birth	1965–74	27	33.3	93	64.5		
	1975–83	10	60.0	120	85.8	0.27	0.13–0.56
Sex	M	21	38.1	103	73.8		
	F	16	43.8	110	79.1	0.21	0.11–0.43
Past Isoniazid Use	Yes	1	0	7	85.7		
	No	36	41.7	206	76.2	0.21	0.11–0.42
Year of Birth and Sex Combined	1965–74 M	15	26.7	50	66.0		
	1965–74 F	12	41.7	43	62.8		
	1975–83 M	6	66.7	53	81.1		
	1975–83 F	4	50.0	67	89.6	0.27	0.13–0.58

misclassification would have resulted in an even smaller relative risk (i.e., higher protective effect). (The mathematical computations to demonstrate the effect of misclassification on the relative risk are available from the author upon request.)

The proportion of potential new cases that were prevented, the "prevented fraction" (PF),[14] is determined by:

$$PF = Pc\ (1-R)/[Pc\ (1-R)+R]$$

where Pc is the estimated proportion of cases that are vaccinated. In this study, Pc = 0.493 and R = 0.39. PF is therefore 0.44, i.e., the vaccination program prevented 44 of every 100 cases that would have occurred in its absence.

According to the 1981 Census of Canada there were 12,195 residents of Indian Reserves in Manitoba aged 0–14 years. The average annual incidence rate of new active tuberculosis for this age group was 136/100,000. Given the relative risk of 0.39, and the proportion of the population who were vaccinated (estimated by the proportions of controls vaccinated) or 0.765, the incidence rate, of tuberculosis among the non-vaccinated was 0.00136/(0.39) (0.765)+(1–0.765), or 0.00255 according to Schlesselman's formula.[15]

The incidence rate among the vaccinated was (0.39) (0.00255), or 0.00099. The risk difference was therefore 0.00255–0.00099, or 0.00156. Thus the average number of cases yearly arising in the Manitoba Indian child population residing in Indian Reserves which can be attributed to non-vaccination (the attributable risk) is (0.00156) (12195) or 19 cases.

Discussion

This study demonstrated that BCG vaccination of newborn Indians in Manitoba offers some protection from the development of tuberculosis in childhood. The protection is not complete: those who received BCG at birth had about 40 per cent of the risk of developing the disease compared to those who did not. The protective effect is thus about 60 per cent.

The only randomized trial of BCG among Canadian Indian newborns was that reported by Ferguson and Sime in Saskatchewan in the 1940s,[16] who demonstrated a protective effect of 80 per cent. During the same period, a trial involving Chicago infants also showed a high degree of protection.[17] There are as yet no case-control studies of the effectiveness of neonatal BCG,[18,19] although a retrospective cohort design used by a group in Manchester[20] demonstrated a protective effect of 75 per cent. Our study, if only bacteriologically confirmed cases were used and if there were no misclassification of BCG status, would also yield a protective effect of over 70 per cent.

There is a possibility that among the controls there may have been undiagnosed cases of tuberculosis. Since only 213 out of over 12,000 eligible individuals, less than 2 per cent, were selected as controls, the probability of selecting an individual who happens to have early undiagnosed tuberculosis is very small, even though the incidence of the disease is high in the Indian population.

Although cases and controls were derived from the same group of communities, we did not adjust for the socioeconomic status of individuals. A satisfactory valid indicator of socioeconomic status among Indians which is sufficiently refined to discriminate between individuals who collectively occupy the low end of most conventional measures has not been adequately developed in Canada. However, one could consider the controls in this study as roughly equivalent to "neighborhood" controls.

Whether 60 per cent protective effect is enough to justify the use of neonatal BCG on a mass scale is a policy issue which cannot be resolved on the basis of this study alone. A cost-benefit analysis, however, can be conducted using some of the data generated in this study. Effectiveness is not the only criterion upon which the decision to launch or continue a mass vaccination program is based. In the Canadian Indian population, the case rate is still some 10 times higher than the Canadian national population. However, the risk of infection (as determined from tuberculin surveys) is not currently known. Tuberculosis epidemiologists prefer the use of the risk of infection rather than the disease or case rate to assess the extent of current transmission of tubercle bacilli in a community.[21,22] In addition, there are other unanswered questions, such as the complication rate from vaccination and the extent of interference of vaccination with case-finding efforts based on the tuberculin test. The decision for the use of BCG vaccination among Indians in Canada is thus considerably more complex than simply resolving the issue of effectiveness.[23]

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