Protective Efficacy of BCG against Leprosy in São Paulo[1]

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The case-control study reported here evaluated the protective effect of BCG vaccine against leprosy in São Paulo, Brazil. Seventy-eight patients under age 16 who had been diagnosed as having leprosy (cases) and 385 healthy individuals (controls) were selected and matched by sex, age, place of residence, and type of exposure to leprosy (intradomiciliary or extradomiciliary). The cases were drawn from an active patient registry and from a group of new leprosy cases treated at 50 health centers in the cities of Bauru and Ribeirão Preto in the state of São Paulo. In order to estimate the protective effect of BCG, the prevalences of BCG scars in cases and controls were compared. The presence of one or more scars was associated with an estimated protective efficacy of 90% (95% confidence interval: 78% to 96%). Stratified analysis by age group, sex, socioeconomic level, and clinical form of the disease revealed no significant differences in the protection provided by the vaccine. However, it seems clear that more data will be needed in order to accurately assess the true relevance of BCG for leprosy control programs.

Leprosy control is based fundamentally on early diagnosis and timely and regular treatment of diagnosed cases. Throughout the years since introduction of multi-drug therapy into leprosy control programs, people have envisaged the possibility of eliminating leprosy as a public health problem in countries where it is endemic. Nevertheless, while one can attribute partial reduction in leprosy's prevalence to multi-drug therapy, its impact upon transmission is unknown. Indeed, the uncertainty associated with leprosy's natural history and transmission mechanisms have thus far precluded the design of effective preventive measures for reducing its incidence.

With regard to vaccines, the principal stumbling block encountered in efforts to develop leprosy vaccines is the inability to culture *Mycobacterium leprae in vitro*. However, by growing *M. leprae* in infected armadillos it has proved possible to develop a number of vaccines of inactivated *M. leprae* associated with BCG. Such vaccines are currently being evaluated in Venezuela, Malawi, and India (*1*).

Because of leprosy's low incidence and long incubation period, designing and implementing field trials for these vaccines is a complex process. Controlled clinical trials have shown that BCG, used initially as a nonspecific immunostimulant as well as an agent of mycobacterial cross-immunity, provides a variable degree of protection against leprosy that

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ranges from 20% to 80% (2–5). This variation in protection, reported by a number of studies, has been attributed to regional differences in the BCG strains used, differing levels of study population exposure, immunity conferred by other mycobacteria prevalent in particular regions, and different genetic susceptibilities of diverse study groups.

Retrospective studies conducted in Venezuela and Brazil have found vaccination with BCG to provide a high degree of protection against leprosy (*6, 7*). These findings, although quite encouraging, must be confirmed in a number of different countries and areas within the Region of the Americas if they are to provide effective support for leprosy policy definition and control strategies. If they are confirmed, plans for eliminating leprosy as a public health problem might call, among other things, for including BCG as an additional tool within the framework of control strategies.

In order to corroborate the protective effect of BCG vaccine against leprosy in Latin America, a case-control study was carried out with children under 16 years of age in the Brazilian state of São Paulo. This article reports the results of that study.

MATERIALS AND METHODS

The study was conducted during 1991 in two São Paulo health regions headquartered in the cities of Bauru and Ribeirão Preto. These regions are classified as having intermediate endemicity (a prevalence of 11.8 cases per 10 000 inhabitants with an annual detection rate of 1.0 per 10 000 inhabitants). Almost 4% of the new leprosy cases detected in São Paulo State are diagnosed in children under 15 years old (*8*).

Intradermal BCG vaccination was first introduced into immunization programs in 1977. Since then coverage rates have remained above 80% for children under 1 year of age. The vaccine employed is produced in Brazil, using the Moreau BCG strain, and is administered in the recommended doses of 0.05 mL for infants up to 90 days (3 months) old and 0.1 mL for children 3 months to 14 years old.

All children under age 16 with diagnosed leprosy cases reported during 1990 were considered eligible to participate in the study, together with all others in this age group with new cases reported during 1991. Appropriate data were obtained from the active case files of the 50 health units participating in the study, and the patients identified were invited to undergo a clinical examination and interview.

For each case of leprosy included in the study, four controls were selected that were matched with the cases by sex, age (± 1 year), and place of residence. The only exceptions were three cases for each of which only three controls could be procured. All of the controls were healthy individuals with an appropriate type of exposure to leprosy. That is, controls selected for cases exposed to intradomiciliary contacts had had exposure to household contacts, while those for cases without intradomiciliary contacts were selected for exposure to extradomiciliary contacts. (To locate extradomiciliary controls, visits were made to a total of 143 families in 40 towns.) This procedure was used to help ensure that cases and controls were comparable with respect to the risk of contracting infection.

All participants were examined by dermatologists from the public health dermatology program and were interviewed by a team of people trained for the purpose. The methods used in conducting the interviews were tested in a pilot study that also served to provide training for members of the team responsible for conducting the main study. During the interview a standard form was used to collect information on each participant's clinical status (extent of any lesions present and skin sensitivity), year of BCG

vaccination, socioeconomic level (monthly family income), and education (years of schooling).

Leprosy cases were classified in terms of the various clinical forms of the disease (i.e., indeterminate, dimorphic, tuberculoid, and lepromatous), using criteria established by the National Program for Control of Hansen's Disease (*9*). Patients who had lepromatous, dimorphic, or indeterminate leprosy and who responded negatively to the lepromin test were classified as multibacillary (MB), while those who had tuberculoid or indeterminate leprosy and responded positively to the lepromin test were classified as paucibacillary (PB).

Confirmation of intradermal BCG vaccination in both cases and controls was obtained by searching out and examining the scar that is typically left by such vaccination on the skin over the deltoid muscle of the right arm.

The 97 cases were compared to the 385 controls with regard to age, sex, education, type of contact, and presence of BCG scars. The chi-square test was used to analyze differences between proportions, while Student's *t*-test was used to compare means. Relative risk was estimated on the basis of the odds ratios (OR) obtained by comparing matched cases and controls (*10*), and 95% confidence intervals (95% CI) were calculated. The efficacy of BCG vaccination was estimated using the formula $E = 1 - OR$, expressing the term $1 - OR$ as a percentage, where E is the efficacy and OR is the estimate of relative risk.

In estimating efficacy, stratified analyses were conducted in order to detect and evaluate any possible differential effect in the various subgroups of the study sample. To assess the existence of an association between the presence or absence of the disease and five variables—age, sex, type of contact, clinical form of the disease, and socioeconomic level—a conditional logistic regression model was constructed. The sample's size was considered sufficient to detect degrees of protection greater than 50% conferred by the vaccine, with a level of statistical significance equal to 5%, assuming a level of BCG vaccination coverage of 70% among controls and vaccine protection of 90%.

RESULTS

In all, data were obtained and analyzed for 97 cases and 385 controls matched with respect to sex, age, and residence. Of the 97 leprosy cases included in the study, 63 were selected from the registry of active cases for 1990, the year preceding initiation of the study, while 34 were new cases diagnosed during 1991, the year the study was conducted. Seven of the cases initially selected were excluded because of an inability to identify controls with which they could be matched. As previously noted, for three other cases only three controls were found. Regarding the type of leprosy involved, 17 cases (17.5%) were classified as multibacillary and 80 (82.5%) as paucibacillary.

Distributions by age, sex, type of contact, education, and number of family members were similar for the cases and controls, no statistically significant differences being found (Table 1). However, only 74.2% of the cases as compared to 95.1% of the controls had at least one scar typical of BCG vaccine; 1% of the cases as compared to 6.8% of the controls had two or more such scars.

The presence of a BCG vaccine scar was inversely associated with the existence of leprosy (OR = 0.10; 95% CI: 0.04–0.22), indicating that an unvaccinated individual's risk of contracting the disease was 10 times greater than that of a vaccinated individual (Table 2). As indicated in Table 3, 52.9% of those with multibacillary cases and 78.8% of those with paucibacillary cases showed BCG vaccine scars.

Table 1. Comparison of the distribution of various characteristics of the 97 study subjects with cases and the 385 controls. São Paulo, Brazil, 1991. SD = standard deviation.

	Controls		Cases		
Characteristics	No.	(% or ±1 SD)	No.	(% or ±1 SD)	*P*
Mean age in years (±1 SD)	*11.7*	*(±2.9)*	*11.8*	*(±2.8)*	*> 0.05*
Age group:					
<10 years	111	(28.8%)	28	(28.9%)	> 0.05
>10 years	274	(71.2%)	69	(71.1%)	
Sex:					
Female	208	(54.0%)	52	(53.6%)	> 0.05
Male	177	(46.0%)	45	(46.4%)	
Type of contact:					
Intradomiciliary	245	(63.6%)	62	(63.9%)	> 0.05
Extradomiciliary	140	(36.4%)	35	(36.1%)	
Schooling in years (±1 SD)	*5.9*	*(±3.3)*	*5.7*	*(±2.9)*	*> 0.05*
Family members (±1 SD)	*5.8*	*(±2.0)*	*5.9*	*(±3.2)*	*> 0.05*
BCG scars:					
0	19	(4.9%)	25	(25.8%)	Chi-square
1	340	(88.3%)	71	(73.2%)	trend
2 or more	26	(6.8%)	1	(1.0%)	< 0.001

Table 2. Leprosy data indicating that the preventive efficacy of BCG vaccination in the study subjects was approximately 90%, using the odds ratio (OR) as an acceptable estimate of relative risk. São Paulo, Brazil, 1991.

	Cases		Controls		
BCG vaccination	No.	(%)	No.	(%)	OR*
Yes	72	(74.2)	366	(95.1)	0.10
No	25	(25.8)	19	(4.9)	(95% CI: 0.04–0.22)
Total	97	(100.0)	385	(100.0)	

*Estimated efficacy of vaccination = E = (1 − OR)% = 90% (95% confidence interval of E = 78% to 96%).

Table 3. Distribution of controls and cases (the latter stratified by the clinical form of leprosy) with regard to presence or absence of a BCG vaccination scar. São Paulo, Brazil, 1991.

			Cases			
	Controls		Paucibacillary		Multibacillary	
BCG vaccination	No.	(%)	No.	(%)	No.	(%)
Yes	366	(95.1)	63	(78.8)	9	(52.9)
No	19	(4.9)	17	(21.2)	8	(47.1)
Total	385	(100.0)	80	(100.0)	17	(100.0)

Table 4. Results of the conditional logistic regression model for estimating the efficacy of BCG vaccination against leprosy. São Paulo, Brazil, 1991.

Characteristics	Controls (no BCG/BCG)	Cases (no BCG/BCG)	E (95% CI)*
Type of contact:			
Intradomiciliary	9/236	14/48	94% (77%–98%)
Extradomiciliary	10/130	11/24	86% (59%–95%)
Sex:			
Female	9/199	11/41	91% (73%–97%)
Male	10/167	14/31	89% (63%–96%)
Clinical form:			
Multibacillary	8/60	8/9	91% (55%–98%)
Paucibacillary	11/306	17/63	90% (74%–96%)
Age group (years):			
<14	11/109	11/19	91% (65%–97%)
≥14	8/257	14/53	96% (80%–99%)
Socioeconomic level:			
Very low	6/88	9/15	89% (58%–97%)
Low	8/211	8/42	80% (36%–94%)
Intermediate	5/67	8/15	88% (1%–99%)

*E = estimated raw efficacy of vaccination = (1 − OR) expressed as a percentage. The estimates of efficacy adjusted with respect to the remaining variables by means of the conditional logistic model did not differ from the unadjusted estimates.

The stratified analysis by type of contact, sex, age group, socioeconomic level, and clinical form of the disease revealed no significant differences in terms of protection provided by the vaccine (Table 4). The estimated raw efficacy of BCG vaccine in the various strata ranged from 80% to 94%; however, the confidence intervals involved were broad, reflecting an estimate imprecision apparently resulting largely from the reduced sample size produced by stratification. The vaccine efficacy estimates adjusted for the remaining variables by means of the logistic model did not differ from the unadjusted estimates.

DISCUSSION AND CONCLUSIONS

The results of studies conducted on the protection provided by BCG vaccine against leprosy and tuberculosis vary from one country to another (*11*). Two studies of BCG's efficacy against leprosy have been conducted in Latin America. The first was a survey of 90 cases and 3 641 controls matched by age, sex, and residence that was conducted in Venezuela during the participant recruitment phase of a controlled clinical trial (*12*). That study estimated that the BCG vaccine's efficacy against leprosy in individuals with one or more BCG vaccination scars was 56% and found that protection increased directly with the number of such scars (*6*). These findings support instructions distributed by the Venezuelan Leprosy Control Program that call for administering BCG vaccine several times to individuals in regular contact with leprosy patients.

The second study was a survey among Brazilian schoolchildren (62 cases and 186 controls) that found the presence of a BCG vaccination scar to be associated inversely with the occurrence of leprosy. The estimated risk that unvaccinated individuals would contract the disease was found to be 5.3 times that of vaccinated individuals, the estimated efficacy of vaccination being 81% (*7*).

Although retrospective studies do not possess the ideal design for evaluating a public health intervention, they have frequently been used to estimate the efficacy of vaccines used by public health services (*10*). In a number of instances controversies have arisen about how to select the best possible controls for case-control studies, in order to avoid bias from differential disease exposure of cases and controls as much as possible (*13, 14*).

The results of the present study are consistent with those reported for the Region of the Americas. The selection of matched controls based on type of contact (intradomiciliary or extradomiciliary) may have reduced possible bias arising from differential case-control exposure. Even so, the data obtained are not immediately useful for formulating recommendations about use of BCG to prevent leprosy. One reason is that the above-mentioned study in Brazil compared BCG vaccination frequencies among children, while in Venezuela the study groups were selected from among the contacts of known patients, including both adults and children (*6, 7*).

The possible existence of differences in terms of the opportunity for exposure to the disease by the various controls selected prevents an immediate inference that active vaccination of individuals in contact with leprosy patients will provide them with the same degree of protection afforded the average control subject. The many unknowns involved in leprosy transmission and the difficulty involved in quantifying certain variables such as time and intensity of exposure could bias the results of virtually any retrospective study. Among other things, socioeconomic and environmental exposure variables that are not adequately controlled in the design or analysis phases can act as confounding factors in the association between the protective effect of BCG and infection with *M. leprae*. These factors are associated not only with risk of contracting the disease but also with access to health services and, accordingly, with vaccination coverage.

Recommendations for conducting public health interventions should be based primarily on the cost-effectiveness and timeliness of such interventions. Before introducing BCG into leprosy immunoprophylaxis, it would be desirable to evaluate the many issues involved in the logistics of the associated interventions, and also to decide which population groups are to be accorded priority in order to optimize the interventions' cost-effectiveness. However, it is not yet known for certain which individuals would benefit most from vaccination. For example, this study's sample size precluded precise estimates of the protection BCG provided to intradomiciliary contacts versus extradomiciliary contacts, and also against the various clinical forms of the disease.

Variances observed in the results of trend analyses and the apparent effectiveness of vaccination have generally been attributed to design differences in the epidemiologic studies conducted and to the frequency and thoroughness of contact examinations (*15*). This illustrates once again the difficulties involved in evaluating the feasibility and benefits of BCG vaccination. In order to evaluate the results of the studies conducted to date and draw acceptable conclusions, it will be necessary to obtain more population-based data. Ecologic studies of the trends observed in the distribution of the various clinical forms of leprosy, their respective incidences, and coverage with BCG vaccination could contribute data that would make it possible to rigorously evaluate the efficacy of BCG in leprosy control programs.

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