Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 6842–6844
Vaccine
www.elsevier.com/locate/vaccine

Short communication

Long lasting BCG protection against leprosy

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Received 25 November 2006; received in revised form 5 June 2007; accepted 19 July 2007
Available online 6 August 2007

Abstract

Background: BCG vaccine protects against leprosy.
Objectives: Estimate BCG protection against leprosy by age by age.
Methods: A case control study with 226 cases of leprosy and 857 controls. BCG vaccination was ascertained via examination of BCG scars. Protection is presented for three age groups.
Results: BCG protection against leprosy was 86% (95% CI: 77–92%) in the age group 18–29; 54% (95% CI: −37% to 85%) in the age group 30–39 and 32% (95% CI: −3% to 56%) in those aged 40 or more.
Conclusions: BCG efficacy against leprosy may well last for three decades and possibly even longer. BCG vaccination must have contributed to worldwide reduction in leprosy incidence.

Keywords: BCG vaccine; Leprosy; Waning of protection; Duration of protection; Vaccine efficacy

1. Background

Leprosy is an infectious, chronic disease caused by *Mycobacterium leprae*. New infections still occur in Africa, Asia and Latin America. WHO reports that in 2005 there were 286,063 prevalent cases worldwide, with 407,791 new cases detected in 2004. Of the new cases detected, about 10% were in children, and just under 5% had a severe disability caused by the leprosy. Brazil has a high prevalence (4 per 10,000 inhabitants) and 10% of the newly detected cases in the world are detected there [1]. BCG vaccination prevents mycobacterial diseases, including leprosy and tuberculosis. Neonatal BCG vaccination is routinely used in most of the world, including Brazil, to prevent tuberculosis. Intra dermal BCG vaccination replaced oral BCG vaccination in Brazil in 1972 [2]. Coverage rates for BCG have been close to 100% in the last 10 years. BCG also protects against leprosy. BCG is a complex vaccine: protection against tuberculosis is known to vary geographically; and against both tuberculosis and leprosy by form of disease. BCG protection wanes with time since vaccination. In fact until recently there was no evidence of BCG protection against tuberculosis lasting more than 10 years [3]. In the past 2 years, there have been three reports of much longer duration of BCG protection, two against tuberculosis [4,5] and one against leprosy [6]. The present paper reports on the protection by age, presumed to reflect protection by time since vaccination offered by BCG against leprosy in a case control study in Brazil.

2. Methods

Methods of the case control study have been published elsewhere [7] but in short, the study was conducted in four municipalities in the state of Ceará, in Northeast Brazil. Cases

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doi:10.1016/j.vaccine.2007.07.032

were adults (over 18) notified with leprosy in the 2 years before the study, who had one of (a) characteristic skin lesion with loss of sensitivity or (b) nerve thickening with loss of sensitivity or (c) *M. leprae* at baciloscopy examination at the reference laboratory (LACEN-CE). Cases were classified according to Ridley and Jopling classification based on the information on the treatment records. All eligible subjects presenting at the health facility for leprosy treatment between March and August 2002 were invited to participate in the study. Four controls per cases were selected from individuals who lived in the same municipality and were aged over 18 presenting to the same health facility for complaints other than skin diseases. Because the original study was investigating novel sources of infection, cases and controls were excluded if they were contacts of a known leprosy case. Cases (226) and controls (857) answered a questionnaire about past exposures, socio-economic environmental and behavioural factors. Of particular interest for this analysis, previous BCG was ascertained by examination of the upper arm for presence of a BCG scar and by history. Analytical methods used and results of the original case control study were described elsewhere [7] but in short, a conditional logistic model was used to investigate the effect of socio-economic, environmental, behavioural, and demographic variables, and of BCG. In the final model the following variables were statistically significant: education, frequency of changing bed linen, history of bathing in open water bodies, and having experienced poverty such that they had had to go without food. Previous BCG vaccination was protective (OR = 0.48), corresponding to a vaccine effectiveness of 52%. Because of the clear BCG protection in adults in the main study we undertook the analysis reported in this paper to investigate BCG protection by age (and indirectly duration of protection). This consisted of repeating the final conditional logistic regression model (including the same variables as the final model above) separately for three age groups: 18–29; 30–39; and 40 and over. Validity of BCG scar reading was estimated comparing presence of scar (the gold standard) with reported information on BCG vaccination, for all groups together and separately for the older age group. The study was approved by the Ethical Committee of the Federal University of Ceará.

3. Results

Table 1 presents validity of scar reading. Overall specificity was 90% (95% CI: 86–92%) and sensitivity: 98% (95% CI 96–99%). For those 40 years or older, the specificity was 83% (95% CI: 77–88%) and the sensitivity was 99% (95% CI: 98–100%). The proportion of controls who had BCG vaccination (which should reflect to a certain degree BCG vaccine coverage in that age cohort) was 81% in those aged under 30; 71% in those aged 30–39 and 32% in those aged over 40. Table 2 presents the number of cases and controls with and without BCG scar for each of the three age groups. Adjusted estimates of BCG efficacy were 86% (95% CI: 77–92%) in the younger age group; 54% (95% CI: −37% to 85%) in the age group 30–39 and 32% (95% CI: −3% to 56%) in the older age group.

Table 1
Specificity and sensitivity of scar reading as an indication of BCG vaccination as reported

	Reported BCG vaccination	Reported no BCG vaccination	Total
BCG Scar	435	51	486
No BCG scar	11	481	492
Total	446	532	978

Table 2
Cases and controls according to BCG scar and age

	BCG scar N (%)		Adjusted VE (95% CI)
Age	Control	Cases	
18–29	184 (81)	19 (44)	86% (77–92%)
30–39	119 (71)	14 (44)	54% (−37% to 85%)
40 or +	148 (32)	37 (25)	32% (−3% to 56%)

4. Discussion

Our results show significant BCG protection against leprosy up to age 30, and an intriguing potential for protection at later ages, although evidence so far is weak. Scar had been shown before to be an excellent indicator of intradermal BCG vaccination in Brazil [8]; this was confirmed in this study. It is unlikely that using scars to indicate previous vaccination introduced errors.

We found that BCG gave very high protection against leprosy (86%) up to age 29. This estimate of protection is well within the range of protection found in three studies undertaken in different states in Brazil in the past: 74% in Manaus, in the North; [9] 81% in States in Central Brazil [10] and 90% in Sao Paulo, in the South [11]. Can we assume that the large majority of vaccinations were given at birth and therefore protection at age up to 29 years corresponds to duration of protection for 29 years? The answer is probably yes for this age group. The National Tuberculosis Control Program introduced neonatal BCG vaccination in Brazil in 1972 [2] and reached very high coverage as the State had a very strong public funded well baby programme with free health care and vaccination. Some of these subjects might have received a second dose: from to 1995 to 2006 the National Tuberculosis Control Program recommended revaccination at ages 7–14; the study did not note the number of scars, only presence or absence. However, the programme was controversial and the coverage for the second dose in the state was very low. So it is very likely that the very high protection observed at ages up to 29 reflects duration of protection for at least 29 years. Until recently, there was no evidence of duration of BCG protection for more than 10 years. Recently two studies reported long lasting protection against tuberculosis mortal-

ity: lasting 60 years in the USA [4] and at least 20 years in Brazil [5]; there is also some recent evidence indicating duration for protection against leprosy lasting up to 30 years [6]. If neonatal BCG protects against leprosy for this long than neonatal BCG must have had an important role in reducing the incidence of leprosy in endemic regions.

Particularly intriguing was the finding of protection against leprosy in those aged 40 and over. It is true that the protection was smaller (32%), and only of borderline significance, but if confirmed this would be of marked relevance. The first issue when understanding this finding is how to interpret the presence of scars in those aged 40 and over. Validity of scar reading is high in this age group, so these must mostly be BCG scars. Subjects in this age group are very unlikely to have received intradermal BCG at birth; the most likely explanation for the presence of BCG scars in adults over 40 is that they were vaccinated later in life, as part of a catch up vaccination (or, much less likely, revaccination). If this is true, the protection associated with a BCG scar in this group cannot tell us much about duration of protection. However the fact itself that subjects aged 40 and over had less leprosy if they had a BCG scar is of interest, independently of when the vaccine was given. Age has an impact on the immune system; this decay is present in innate and in adaptative immune response [12]. Is it possible that having received BCG can reduce this decay? This is consistent with the role of BCG in stimulating interferon production, and would explain both this finding and the lower mortality by tuberculosis 50 years after BCG vaccination in the trial in the USA.

Finally, this was a case control study and as such potentially subject to bias. Recall bias is unlikely as scar was examined and validity of scar was so high. We excluded cases and controls with a known leprosy contacts, restricting the study population to people without known leprosy contacts. Although the reason for this exclusion was not related to BCG vaccination, by doing so we avoided the possibility that the proportion vaccinated was distorted by vaccination triggered by contact tracing; the proportion vaccinated in controls in this study is likely to reflect that in the population producing the cases, excluding selection bias. Finally, ascertainment of controls from health facilities may bias upward the estimate of efficacy of interventions delivered at the health facility [13] but again this would not have an impact in this study as BCG is given at birth in maternity wards.

In conclusion, our results show that the effect of BCG protection against leprosy can last at least for 30 years; and suggests – although evidence is weak – that it may possibly last for over 40 years; the effect for the first 29 years is very high, over 85%. This adds to the new and growing evidence that BCG protection against tuberculosis and leprosy can last much longer than previously believed. Finally, adults over 40 with a BCG scar may have lower risk of leprosy, and further research should investigate potential mechanism for that protection.

Acknowledgements

The authors acknowledge the CNPq (#620168/2004-8) and CAPES (#0119/01-6) for supporting this project.

References

[1] http://dtr2001.saude.gov.br/svs/epi/hanseniase/hansen_00.htm.
[2] Benevolo-de-Andrade TC, Monteiro-Maia R, Cosgrove C, Castello-Branco LR. BCG Moreau Rio de Janeiro: an oral vaccine against tuberculosis—review. Mem Inst Oswaldo Cruz 2005;100(5):459–65.
[3] Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? Int J Tuberc Lung Dis 1998;2(3):200–7.
[4] Barreto ML, Cunha SS, Pereira SM, Genser B, Hijjar MA, Yury IM, et al. Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil. Int J Tuberc Lung Dis 2005;9(10):1171–3.
[5] Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60-year follow-up study. JAMA 2004;291(17):2086–91.
[6] Zodpey SP, Ambadekar NN, Thakur A. Effectiveness of Bacillus Calmette Guerin (BCG) vaccination in the prevention of leprosy: a population-based case-control study in Yavatmal District, India. Public Health 2005;119(3):209–16.
[7] Kerr-Pontes LR, Barreto ML, Evangelista CM, Rodrigues LC, Heukelbach J, Feldmeier H. Socioeconomic, environmental, and behavioural risk factors for leprosy in North-east Brazil: results of a case-control study. Int J Epidemiol 2006.
[8] Pereira SM, Dourado I, Barreto ML, Cunha SS, Ichiara MY, Hijjar MA, et al. Sensitivity and specificity of BCG scar reading in Brazil. Int J Tuberc Lung Dis 2001;5(11):1067–70.
[9] Cunha SS, Rodrigues LC, Pedrosa V, Dourado IM, Barreto ML, Pereira SM. Neonatal BCG protection against leprosy: a study in Manaus, Brazilian Amazon. Leprosy Rev 2004;75(4):357–66.
[10] Rodrigues ML, Silva SA, Neto JC, de Andrade AL, Martelli CM, Zicker F. Protective effect of intradermal BCG against leprosy; a case-control study in central Brazil. Int J Leprosy Other Mycobact Dis 1992;60(3):335–9.
[11] Lombardi C, Pedrazzani ES, Pedrazzani JC, Filho PF, Zicker F. Protective efficacy of BCG against leprosy in Sao Paulo. Bull Pan Am Health Organ 1996;30(1):24–30.
[12] Prelog M. Aging of the immune system: a risk factor for autoimmunity? Autoimmun Rev 2006;5(2):136–9.
[13] Dantas OM, Ximenes RA, de Albuquerque MdeF, Montarroyos UR, de Souza WV, Varejao P, et al. Selection bias: neighbourhood controls and controls selected from those presenting to a Health Unit in a case control study of efficacy of BCG revaccination. BMC Med Res Methodol 2007;7:11.