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Short communication

Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: Second report of the BCG-REVAC cluster-randomised trial

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ABSTRACT

BCG revaccination is still used in some tuberculosis endemic countries. Until now, the little evidence available suggested that BCG revaccination confers very limited additional protection, although there was no information on whether protection depends on the setting and age of revaccination, or if protection increases with time since vaccination. Here we report on an extended follow up of the BCG-REVAC trial, a cluster randomised trial conducted in the Brazilian cities Salvador and Manaus including over 200,000 children aged 7–14 years aimed to evaluate the efficacy of BCG revaccination in children who had received neonatal BCG vaccination. With the extended follow-up (9 years) and the additional cases accrued we now have enough power to report vaccine efficacy separately for the two cities (with different distances from Equator and presumably different prevalence of non-tuberculosis mycobacteria), and by age at vaccination and clinical form. The overall vaccine efficacy was 12% (−2 to 24%) as compared to 9% (−16 to 29%) for the 5-year follow up. Vaccine efficacy was higher in Salvador (19%, 3 to 33%) than in Manaus (1%, −27 to 27%) with the highest vaccine efficacy in children from Salvador aged <11 years at revaccination (33%, 3 to 54%). The findings are in line with the hypothesis that BCG vaccination offers higher efficacy in low NTMb prevalence, and show that revaccination with BCG can offer weak protection in selected subgroups.

1. Introduction

Tuberculosis (tb) is one of the leading causes of death in the developing world [1]. BCG vaccination in the first year of life offers excellent protection against extra pulmonary forms of tuberculosis (EPTB) in childhood [2] but protection from pulmonary tuberculosis (PTB) varies from 0 to 80% [3]. WHO recommends neonatal BCG vaccination [4] which is routine in many countries [5]. The evidence so far suggested that revaccination confers no additional protection to neonatal vaccination. In Malawi, a trial of the effect of a second BCG vaccination in children and adults showed no protection against tuberculosis [6]. The BCG REVAC trial focusing on school aged children, conducted in Brazil and reported in 2005 also showed no additional protection of a second BCG vaccination against tuberculosis (VE 9% (−16 to 29%)) or leprosy [7,8]. It is not known whether protection given by a second BCG vaccination would vary according to the setting or the age at revaccination; or if protection will be higher with longer follow up after revaccination. After an additional 4 years of follow up, the BCG REVAC trial has now increased power to detect differences in the vaccine efficacy between different settings and age groups.

2. Material and methods

The BCG-REVAC cluster randomised trial had the objective to estimate the vaccine efficacy of BCG revaccination. The number of cases during the first 5 years of follow up was too small to allow subgroup analyses [7]. However, the 486 cases accrued from an additional 4 years of follow up now provide sufficient power for more detailed analyses. A description of the study design [9],

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validity of scar reading [10] and adverse events were presented elsewhere [11]. Briefly, the BCG-REVAC trial was conducted in two Brazilian cities: Salvador and Manaus. One of the reasons offered for the variation in BCG efficacy is variations in prevalence of non-tuberculosis mycobacteria, which is correlated to latitude [12]. The cities were chosen to make it possible to investigate whether BCG vaccine efficacy is different in cities with different latitudes [12]. Manaus is situated near the Equator with a high temperature and humidity and presumably a high prevalence of non-tuberculosis mycobacteria (NTMb)[13]; Salvador lies further away from the Equator and has a low prevalence of NTMb. Stratified randomisation (with strata of similar socio-economic characteristics and incidence of tuberculosis/leprosy) was used to allocate 763 schools to intervention arm and control arm. In each arm children's BCG vaccination status was assessed by BCG scar reading and baseline information was collected. The study population to assess the efficacy of revaccination consisted of children aged 7–14 years with one BCG scar only before revaccination (n = 200,805 children). In the intervention arm 103,718 children were vaccinated with the Moreaux strain (Rio de Janeiro); 97,087 children received no intervention and formed the controlled group. The trial was open-label with no placebo. Participants were able to "opt out" – i.e. parents of children in schools allocated to the intervention arm were given information about the trial and the vaccination and could withdraw their children. Details of the study population and the recruitment process have been described previously [7].

We identified cases via the Brazilian Tuberculosis Control Programme, the only provider of tuberculosis treatment in Brazil. Cases were validated by independent physicians and linked to the study population.

The incidence of tuberculosis was the primary outcome. We used a Poisson regression based on generalised-estimating-equations (GEE) suitable for overdispersed data [14] to calculate the incidence rate ratio (IRR) and calculated vaccine efficacy as (1 − [rate of tb amongst vaccinated/rate of tb amongst unvaccinated children]) × 100. Calculation of the IRR was controlled for socio-economic status, incidence of tuberculosis and leprosy, sex, age at vaccination and age at diagnosis. Age at diagnoses was modelled as a time-dependent variable.

The ethics committee of the University Hospital, Universidade Federal da Bahia and the ethics committee of the London School of Hygiene and Tropical Medicine approved the trial. The trial is registered with an International Standard Randomised Controlled Trial Number, ISRCTN07601391 (http://www.controlled-trials.com/ISRCTN07601391).

3. Results

These are the results of the 9-year follow up of children revaccinated at school age. Baseline data on the individual and cluster characteristics and children excluded from the analysis have been described previously [7].

There were 765 cases of tuberculosis in this analysis: 378 in the intervention group and 387 in the control group, a higher incidence than in previous years given the increase in incidence of tuberculosis in young adults. Table 1 shows the number of pulmonary and non-pulmonary tuberculosis cases by age of vaccination and by study site.

The estimated number of person years of follow up was 1,806,558; 933,107 in the intervention and 873,451 in the control group. The crude incidence of tuberculosis was 41.6 per 100,000 person years in the intervention group and 45.5 per 100,000 person years in the control group (Rate ratio 0.91, 0.79–1.05). There was no evidence for a design effect when comparing parameters between the naïve and the GEE regression model.

Table 1
Efficacy of a second BCG dose at school age (VE in %), total and stratified by city, clinical form and age at vaccination.

	7–10 years						11–14 years						Total					
	Cases			Efficacy estimate			Cases			Efficacy estimate			Cases			Efficacy estimate		
	Int	Con	Tot	VE	95% CI	p-Value	Int	Con	Tot	VE	95% CI	p-Value	Int	Con	Tot	VE	95% CI	p-Value
Salvador																		
Pulmonary cases	45	57	102	32	0–53	0.051	161	128	289	10	−14 to 39	0.372	206	185	391	17	−2 to 32	0.070
Non-pulmonary cases	5	7	12	39	−91 to 80	0.398	25	25	50	28	−25 to 59	0.238	30	32	62	31	−12 to 58	0.131
All cases	50	64	114	33	3–54	0.034	186	153	339	13	−8 to 30	0.199	236	217	453	19	3–33	0.022
Manaus																		
Pulmonary cases	33	30	63	−17	−102 to 32	0.559	79	105	184	8	−26 to 33	0.606	112	135	247	1	−32 to 25	0.961
Non-pulmonary cases	11	8	19	−61	−297 to 35	0.298	19	27	46	9	−62 to 49	0.753	30	35	65	−3	−68 to 38	0.920
All cases	44	38	82	−25	−101 to 32	0.359	98	132	230	9	−20 to 31	0.522	142	170	312	1	−27 to 23	0.932
Both cities																		
Pulmonary cases	78	87	165	17	−14 to 39	0.257	240	233	473	10	−8 to 26	0.263	318	320	638	12	−4 to 25	0.136
Non-pulmonary cases	16	15	31	−1	−104 to 49	0.967	44	52	96	20	−20 to 46	0.280	60	67	127	14	−22 to 40	0.388
All cases	94	102	196	13	−17 to 35	0.359	284	285	569	12	−5 to 26	0.149	378	387	765	12	−2 to 24	0.088

Estimate of vaccine efficacy intervention vs. control group from a GEE Poisson regression model adjusted for age, sex, socio-economic status, incidence of leprosy and incidence of tuberculosis.
Int, intervention; Con, control; Tot, total; VE, vaccine efficacy

Table 1 shows the vaccine efficacy (VE) according to study site and age at diagnosis. Revaccination was protective in Salvador (VE 19%, 3–33%) but not in Manaus (VE 1%, −27 to 23%). In Salvador only children aged <11 years at vaccination where protected (VE 33%, 3–54%). For both cities combined, weak evidence of a protective effect was found ($p = 0.08$); although the combined measure is of difficult interpretation.

4. Discussion

Efficacy of BCG revaccination presented a small not significant increase with time of follow up, from 9% (−16 to 29%) at 0–5 years of follow up to 12% (−2 to 24%) at 0–9 years of follow up. Efficacy was almost 20% in Salvador, and practically zero in Manaus; it was higher when given at younger age. Although this finding could be due to chance considering the large and overlapping confidence intervals, it was unexpected: we expected efficacy of revaccination to increase with age at vaccination as efficacy of neonatal BCG decreases. A possible explanation is that infection with *Mycobacterium tuberculosis* (*M. tb*) increases with age. In fact, in the study population from Salvador positive PPD results increased from 14.5% in children aged 7–8 years to 28% in children aged 13–14 years [15].

The difference in VE between the two cities was in the direction expected, based on the fact that Manaus is closer to the Equator and presumably has higher prevalence of *M. tb* and NTMb [3]. Different infection rates with *M. tb* prior to revaccination could also explain the different vaccine efficacies between the study sites. Infection with *M. tb*. reduces the protective effect of the BCG vaccine [12].

The follow up of this trial will continue to accrue power to confirm the effect modification by city and age at vaccination, and detect differences in the vaccine efficacy for PTB and EPTB. Regarding the overall vaccine efficacies, however, it seems that BCG revaccination confers a similar protection on the two different clinical forms of tuberculosis.

5. Conclusions

An additional 4 years of follow up of children revaccinated with BCG at school age showed that revaccination can offer additional protection, although protection was restricted to Salvador, the site further from the Equator, and confined to a small subgroup of children aged <11 years at vaccination.

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Contributors: L.C.R., M.L.B. were involved in designing the study, supervising field work, data analysis and interpretation and editing the manuscript; S.M.P., S.S.C., M.Y.I. were involved in field work, interpretation of results and editing the manuscript; D.P. contributed to the analysis, interpreted the results and wrote the manuscript; A.A.C., C.S'.A. were involved in clinical supervision, interpretation of results and editing the manuscript; BG led the analysis, and was involved in the interpretation of results and editing the manuscript. All authors had access to all data in the study and held final responsibility for the decision to submit for publication. *Role of the funding source*: Neither of the two funding bodies had any role in the study design, data collection, data analysis, interpretation of the results or the writing of the report. All authors had full access to the data of the trial (except allocation to intervention or control) at all times. Decisions to publish data of the trial are the shared responsibility of all authors.

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