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Design paper

Design of the Brazilian BCG-REVAC trial against tuberculosis: a large, simple randomized community trial to evaluate the impact on tuberculosis of BCG revaccination at school age

Mauricio L. Barreto, M.D., M.P.H., Ph.D.[a,*], Laura C. Rodrigues, M.Sc., Ph.D.[b], Sergio S. Cunha, M.D., M.P.H.[a], Susan Pereira, M.D., M.P.H.[a], Miguel A. Hijjar, M.D.[c], Maria Yury Ichihara, M.D., M.P.H.[a], Silvana C. de Brito, B.Sc.[a], Ines Dourado, M.D., M.P.H., Ph.D.[a]

[a]*Instituto de Saúde Coletiva, Universidade Federal da Bahia, Salvador, Bahia, Brazil*
[b]*London School of Hygiene and Tropical Medicine, London, England*
[c]*Centro de Referência Helio Fraga, FUNASA/Ministry of Health, Rio de Janeiro, Brazil*

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Abstract

This paper describes the design and baseline results of a large and simple randomized controlled trial of the protection against tuberculosis of a dose of Bacillus Calmette Guerin (BCG) vaccination given to school children in a population with a high coverage of neonatal BCG (The Brazilian BCG-REVAC trial). The study started in 1996 and is a pair-matched and stratified-cluster randomized controlled trial with no placebo. The study population consists of children aged 7–14 years enrolled in 763 state schools from the cities of Salvador and Manaus, Brazil. Schools were the unit of randomization. Identifying information was collected for 354,708 school children. The final study population, after exclusions on the basis of age, BCG scar readings and absence from school on the day of the study visit, consists of 242,401 children, of whom 125,403 are in intervention schools. Follow-up relies on ascertainment of cases diagnosed at the health services and notified to the tuberculosis control program surveillance system. Blindness is guaranteed during linkage and validation of cases. Analysis is planned for the next 12 months, where efficacy will be estimated by calculating incidence of tuberculosis in the vaccine and control groups, taking into consideration the cluster design. The intervention

* Corresponding author: Prof. Mauricio L. Barreto, Instituto de Saúde Coletiva, Universidade Federal da Bahia, Rua Padre Feijo, 29, 40.110-179 Salvador, Bahia, Brazil. Tel.: +55-71-332-5137; fax: +55-71-237-5856.
E-mail address: mauricio@ufba.br

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studied, a second BCG vaccination, is widely used, although the World Health Organization does not recommend it on the basis of absence of evidence of protection or lack of protection. The results of the trial will make it possible for BCG revaccination practice to be informed by evidence. This is an example of a large simple and relatively inexpensive effectiveness trial, resulting from good collaboration between academia and health and education services enabling developing countries to define policies that are relevant for their reality.

Keywords: BCG; Bacillus Calmette-Guerin; Revaccination; Protective effect; Cluster randomization; Tuberculosis; Randomized clinical trial; Brazil

Introduction

Tuberculosis is one of the ten main causes of death in the developing world [1]. It is estimated that one third of the world population is infected with *Mycobacterium tuberculosis* and that each year there are 8 million new cases and 1.9 million deaths [2]. The incidence of tuberculosis is not decreasing as fast as it did in the past, maybe reflecting the impact of AIDS and growing inequality in some places [3]. Early detection and treatment of cases is the main strategy in the control of tuberculosis, but there is also a vaccine, Bacilus Calmette-Guerin (BCG). Neonatal BCG has been used as part of the effort to prevent tuberculosis, and most countries reached a high coverage in the early 1980s [4]. BCG efficacy against tuberculosis has been evaluated in several randomized trials [5]. The efficacy against pulmonary forms of tuberculosis in the trials ranged from negative to very high. Of the many hypotheses offered to explain the variation in efficacy, the most influential is that efficacy is lower when prevalence of atypical mycobacteria is high [5]. There is, however, striking consistency in the effect of BCG against tuberculosis meningitis, with protection estimated to be over 80% [6].

Despite great efforts invested in tuberculosis control, tuberculosis remains an important health problem in several parts of the world, including Brazil. In Brazil the incidence of notified cases of tuberculosis is relatively high, about 50 new cases per 100,000 per year, and has remained stable over the past 10 years. Three case-control studies have shown that neonatal BCG vaccination is highly protective against tuberculous meningitis in Brazil [7–9]. As part of the effort to control tuberculosis in Brazil, in 1994 the Ministry of Health recommended the vaccination of school-aged children with BCG [10]. For most children this would be a second dose of BCG, given the high neonatal BCG coverage. The rationale for the recommendation was that the tuberculosis incidence in Brazil increases sharply in young adults as the effect of BCG wanes over time [11] and that it is not known whether a second dose of BCG gives additional protection [10]. The recommendation quoted time-trend analysis of routine data in Hungary, where there was a decline in incidence after revaccination was introduced; from Poland, where those not receiving a second dose of BCG had a higher incidence of tuberculosis; and a small case control study in Chile with no protection. Since then a meta-analysis of previous trials of the effect of a first dose of BCG on tuberculosis showed a decay of the effect over time [11]. The year after the Brazilian document was published, a joint statement from the World Health Organization Global Programmes on Tuberculosis and on Vaccines opined that there was no scientific basis to recommend repeat BCG schemes [12]. This was

also based on the absence of conclusive evidence on the effect or lack of effect of a second dose of BCG. Since then, a trial of the effect of a second BCG dose was reported, with 50% protective effect against leprosy but no effect against tuberculosis [13]. This, however, was undertaken in Malawi, where a first dose of BCG had shown no protection against tuberculosis [14]. BCG revaccination is given routinely in some countries and is a common policy in Eastern Europe [15]. There is no good immunological marker of protection against tuberculosis, and estimation of protection requires field trials with disease endpoints.

Brazil is a federation of states, and the Federal governmental agencies only make recommendations for the vaccination program. The states have a degree of autonomy in choosing whether to implement each recommendation. When the Brazilian Ministry of Health recommended BCG revaccination, several state health departments questioned the recommendation in the face of conflicting advice and lack of evidence. This created an opportunity to implement the intervention in a randomized way to enable the evaluation of its impact.

In this paper, we present an overview of the methodological and operational aspects of the trial, which started in 1996, and has as the main objective to estimate the efficacy of BCG vaccination of schoolchildren against tuberculosis, in a population with a high coverage of neonatal BCG. We also present baseline characteristics of the trial population. A second major objective is to estimate the efficacy against leprosy, still an important population health problem in some areas of the country. The additional procedures implemented in Manaus to meet the second objective, including the sample size required for estimating the efficacy against leprosy, will be reported in a separate paper. A long-term objective is to compare BCG protection against tuberculosis in two sites, one with high and one with low prevalence of atypical mycobacteria. This will rely on continued follow-up after first analysis; the duration of extended follow-up will depend on any observed protection.

Study design

Overview

This trial was designed to be large enough to allow for estimation of a level of protection of public health importance in a reasonable period of time; to approximate routine conditions of vaccine delivery, including ascertaining in the study all children who would be eligible for vaccination in the routine program; to minimize costs by using a simple design and existing facilities for vaccine delivery, surveillance of adverse events and ascertainment of cases and to be robust and convincing enough to influence policy decisions in Brazil and similar countries. Clemens et al. proposed vaccine trials with these characteristics and called them effectiveness trials, as opposed to efficacy trials, which operate under more restricted experimental conditions and estimate maximum protection under ideal conditions rather than protection achieved under routine conditions [16].

This is a randomized controlled field trial with no placebo. The study population consists of children enrolled in state schools. Criteria for exclusion of schools in the two cities were being a private school, being located in the rural areas of the cities, being a school for children with special needs, being closed for building renovation during the study implementation or having fewer than 50 students. These exclusions were for logistic or ethical reasons

and preceded randomization. All healthy children were considered eligible. Schools were the unit of randomization. Identifying information was collected for all children in the schools and double entered in the study database. Children were vaccinated at schools. Cases in our study area and age group diagnosed by the tuberculosis control program and notified to the surveillance system are identified by the study team. Outpatient and hospital records of these cases of tuberculosis are abstracted and validated by two experienced chest physicians. Cases are linked to the study population in the study database. The validation and the link are made blind to vaccination status.

Fieldwork started in June 1996. The trial is a collaboration between the Universidade Federal da Bahia and the London University, with support from the Brazilian Tuberculosis Control and Brazilian Immunisation Programmes, the state and city department of health and education and Brazilian medical scientific societies. The trial advisory scientific committee, which includes academic epidemiologists and chest physicians and representatives of the Brazilian Ministry of Health, monitors progress and gives technical and scientific advice.

Setting

The trial is being conducted in two sites: the city of Salvador, capital of the state of Bahia, and the city of Manaus, capital of the state of Amazonas. The study started in Salvador in 1996. At that time, the city had a population of 2.2 million. In Manaus, fieldwork started in 1998, when the population was 1.2 million. Manaus has higher humidity than Salvador, and it is generally assumed (although data on this is scarce) that prevalence of infection with atypical mycobacteria is higher.

Age-specific tuberculosis incidence is similar in the two cities. Table 1 shows the number of children aged 7–19 years in Salvador and Manaus in 1996, as well as the number of cases and rates of tuberculosis in that age group. As expected there was a marked increase in incidence of tuberculosis in young adults.

Sample size

The sample size was calculated as that necessary to estimate the protection conferred by a dose of BCG given to schoolchildren, irrespective of whether they received neonatal BCG. Some children would already have been infected with tuberculosis by the time they received BCG at school. The effect of a positive purified protein derivative (PPD) on rates of disease, the implications for studies of BCG vaccine efficacy and tables for sample size calculations

Table 1. Population, number of cases and incidence rates (per 100,000) of tuberculosis by age in the cities of Salvador and Manaus, Brazil, 1996

	Salvador			Manaus		
Age	Population	Cases	Incidence	Population	Cases	Incidence
7–10	171,407	31	18.1	107,988	14	12.9
11–14	202,515	62	30.6	117,925	39	33.1
15–19	267,054	293	109.7	151,347	205	135.4
Total	640,976	386	60.2	377,260	258	68.8

Source: Health Departments of the States of Bahia and Amazonas.

considering these factors are presented by Smith [17]. We followed the recommendation of the paper and did not try to identify infected children, but adjusted the sample size to take that into account. We assumed that 30% of the children would have been infected by the time they received vaccination in the trial. Because of public health reasons, we were not interested in a protection rate below 50% in uninfected children. According to the tables provided by Smith these parameters would result in a protection rate of 30% in the population as a whole [17].

Sample size was calculated based on the mean notification rate for all forms of tuberculosis in Salvador and Manaus in the age group 7–19 years. Incidence rises sharply with age, and we expected the incidence to rise with increasing time of follow-up as the study children aged. For a power of 80%, precision of 95%, observed protection of 30%, and intervention and control groups of the same size, the required sample size was, for an average incidence of 20/100,000, about 774,000 years of follow-up in each group; for an average of incidence of 30/100,000, about 516,000 years of follow-up in each group and for an average incidence of incidence of 40/100,000, about 387,000 years of follow up.

We then considered two additional factors: the pair-matched cluster randomization and the validation of cases. Tuberculosis is a rare disease, and we expected an average well below one case per school. When there is only one case per cluster, the design effect is small, with no need to increase the sample size. Schools were pair-matched for variables associated with incidence of tuberculosis to make incidence similar. We did not expect all cases to be confirmed at validation (preliminary results show less than 2% of cases not being validated). We decided that we required a flexible sample size estimate: a feasible number of schools with a range of potential years of follow-up, to be longer or shorter as needed. There are intervention and control groups of 150,000 children each, with an expected follow-up period between 2.5 and 5 years. The incidence of validated tuberculosis cases will be monitored (blind to allocation), and on that basis the decision will be made on when to undertake the first analysis.

Selection and randomization of schools

The departments of education in the two cities are active partners in the trial and helped to organize meetings with the head teachers to discuss the project. They also provided the study team with a list of all state schools and with addresses and the number of students in each school. Schools were linked to census information based on the school's address. Geographical, demographic and health information was then used to classify schools in strata. Pairs of schools (those with most similar number of students, to make the number of students allocated to each arm similar) were identified within strata, and in each pair one school was allocated at random (using computer-generated random numbers) to vaccination and the other to the control group. Schools without a pair were allocated at random. Different information was used to define the strata in Salvador and Manaus using what data was available and reflecting the fact that the trial was evaluating efficacy of BCG against tuberculosis and leprosy in Manaus but against tuberculosis only in Salvador.

In Salvador, strata were defined based on data from census information zones (ZI) of on average 30,000 people. The study team established that there was an association at ZI level

between rates of notified tuberculosis and proportion of households with monthly income below five times the minimum wage (about US$ 375). ZIs were grouped in four strata, using proportion of households with monthly household income below five times the minimum wage from 0–25%, 26–50%, 51–75% and over 76%. Schools were linked to a ZI based on the school's address and allocated to one of the four strata based on the ZI to which they were linked. In Manaus, where the study includes a component estimating BCG efficacy against leprosy, schools were linked to administrative areas of on average 20,000 inhabitants for which data were available on incidence of tuberculosis and leprosy. These areas were classified into four strata according to whether they had high or low incidence of tuberculosis and leprosy. A fifth stratum was created for areas with information missing on incidence of tuberculosis, leprosy or both. The administrative areas were grouped into five administrative regions. Within each stratum, schools were grouped in the administrative regions. Each school was paired to another school in the same stratum and region, based on the similarity of the number of students registered (to make the total number of school children in each allocation group similar).

The intervention

There were four components to the implementation of the trial: recruitment, ascertainment of previous vaccination status, BCG vaccination of the intervention group and surveillance of adverse events in the intervention group. The school year is organized in two semesters in Brazil, and fieldwork was conducted when schools were open. The first semester starts in February and ends in June; the second starts in July and ends in November. Recruitment and vaccination activities started in Salvador in September 1996, stopped during Christmas holidays, resumed in February 1977 and ended in June 1997. In Manaus fieldwork started and ended during the second semester of 1998.

Recruitment and information from and to parents

Recruitment was undertaken by clerks who visited each school and collected the following data on each student registered in the school: full name, date of birth, sex, address, classroom, and full name of the mother. In this paper we will refer to these children as the children in the database. This was done without contact with students, by transcribing data from school records into a standard form. In schools allocated to vaccination an information pack was given to children to take to their parents. This contained a leaflet with information on the trial and on what to do in case of adverse reactions, and a request for information on previous BCG vaccination and for the child to bring the vaccination card (if still kept) for examination by the study team. A form was also given, to be signed by parents/guardians who wished to withdraw their children from the study.

Ascertainment of previous BCG vaccination status

Although not relevant for the main study question, information on previous BCG was obtained from three sources: the form completed by parents on history of BCG, the vaccination card and scar reading by the study team. Information from the first two sources was abstracted

in a standard form and was only obtained from children in schools allocated to vaccination. Children in both types of schools had their BCG scar read by examination of the deltoid area of the right arm, but this was done differently in schools allocated to vaccination and to the control group. The clerk team visited schools in the control group and ascertained the presence of BCG scar in all children present at school on the day of the visit. Two different clerks examined a sample of children blindly to estimate the reliability of scar reading. The vaccination team visited the schools allocated to vaccination and read the scars in all the children present on the day of the visit for the vaccination. After reading the scar, they abstracted information on previous BCG from the parental form and the vaccination card for those who brought the form or the card.

Vaccination

The study employed seven vaccination teams in Salvador and four in Manaus, each with one nurse, four auxiliary nurses and four clerks. Children with two scars, with unclear scar reading, those whose parents requested that the children be withdrawn from the study and children who themselves refused to be vaccinated were not vaccinated. Children absent on the day of the visit (for whatever reason) were not vaccinated. BCG vaccination was done by a trained nurse through intradermic injection in the deltoid region of the arm. Vaccine was applied below the scar in children with a scar by the team's nurse. The vaccines were stored in adequate conditions at a central vaccine storage facility in the state health department and delivered to the campaign headquarters when required. The vaccines were kept refrigerated and the temperature checked regularly. The vaccine used was a lyophilized BCG produced by Ataulfo de Paiva Foundation (Rio de Janeiro, Brazil) using a Moreau strain. This is the vaccine used by the Brazilian National Programme of Immunisation and has been shown to offer high protection against tuberculous meningitis in Brazil [7–9]. A vial with 50 doses was specially produced for this study (the usual vial has 10 doses).

Surveillance of adverse events

The trial did not set up an active surveillance system to follow up adverse events, as BCG revaccination was an official recommendation, and no placebos were used. However, the study did take actions to enhance routine passive surveillance. A letter containing information on BCG adverse events was distributed to every child on the day of vaccination, encouraging parents to take their children to a health facility if in the weeks following vaccination they had an adverse event consistent with a reaction to BCG vaccination. Family members, teachers and staff in the health facilities were advised to contact the project investigators directly or by phone to report such cases.

Follow-up procedures

Building up the study database

All data collected on each child at registration were entered in a database, to be used for linkage of cases during follow-up. The database was created for easy access to information for identification of children, but the information on whether the child was allocated to a vac-

cine or control group, and on whether the child received the vaccine or not, was protected with a password system. There are 351,951 children in the database, 156,092 in Manaus and 195,859 in Salvador. This corresponds to 54% of all school-aged children in Salvador and 69% in Manaus. The children not in the study are not registered in a school (e.g., street children, homeless children) or are registered in schools not included in the study (private schools, schools in rural areas, schools for children with special needs, schools under renovation during the implementation or small schools with fewer than 50 students).

Ascertainment of cases

Ascertainment relies on identification of cases by the tuberculosis control program in the two cities. The study team believed, based on the experience of public health staff in the area, that the identification of cases by the control program/surveillance system was good enough to serve as the mechanism for ascertainment of cases in the study. Notification of cases of tuberculosis is compulsory. Diagnosis and treatment of tuberculosis is free, but even the few cases that choose to receive their medical attention in private services need to be referred to the tuberculosis program to collect medicines as these are not commercially available.

Links were established with the tuberculosis control program and the surveillance system in the two cities to speed up the study team's access to information. These resulted in arrangements with the central information units/surveillance system from both health departments and in the main health facilities in charge of diagnosis and treatment of tuberculosis to send to the study team information on all diagnosed cases in the target age group and resident in the two cities. The range of birth dates used at this stage is wider than that in the study population to avoid failing to ascertain study children because of wrong month or day of birth. Telephone contact is made periodically between the offices and frequent visits are made to the unit, health facilities diagnosing tuberculosis and to the laboratories performing sputum cultures for *M. tuberculosis* to review the registration of new cases and monitor the flow of information to the study team.

Linkage of cases to the database

The names of children with reported tuberculosis with a date of birth and area of residence consistent with our study population are searched for in the study database. The search is blind to the vaccination status of the children. Linkage is made for each individual case using name of the child, name of the mother, sex and date of birth of the child, and it consists of two steps. The first is an automatic selection of all children in the database with similar characteristics to those of the case. The second step is a manual linkage, based on a subjective decision on which, if any, of the selected children is a match for the case. Most of the children linked so far are perfect matches, with complete concordance on all variables. Some matches are not perfect. To be acceptable as a link, there needs to be concordance on sex and year of birth and the names of mother and child must be extremely similar, although not necessarily identical.

Validation of cases

Two chest physicians independently review all cases of tuberculosis based on information abstracted from the notification form and from the chest clinic record, including copies of all

exam results and X-ray reports, and when available, a copy of the X-ray itself. The validation is done blind to whether the child was allocated to a vaccine or control school and to PPD result. Cases are classified subjectively by each of the two chest physicians into confirmed, probable (enough information in the record to justify introduction of treatment for tuberculosis), suspected (not enough information to judge) and excluded (enough information in the record to justify not treating with antituberculosis drugs). After all cases are classified, a third specialist reviews those classified differently by the two chest physicians.

Concealment of allocation

There was no use of placebo and no concealment of allocation in the intervention phase. Diagnosis of tuberculoses is done by the routine service and therefore not blind. Validation of cases and linkage between cases and study subjects is done blind to the vaccine status of subjects.

Analysis

The proposed main analysis includes the estimation of the efficacy of BCG against tuberculosis overall in the first instance; continued follow-up is planned to enable estimation of efficacy for vaccination at two age groups, for the two cities and for those who had one BCG scar. The design effect will be calculated and used to correct the 95% confidence intervals (CIs).

Analysis will be restricted to children present at school when the team visited (identifiable by having had a BCG scar reading by the study team) and who had one or no BCG scars. We call these children "the study children." The reason to restrict the analysis to these children is that in vaccinated schools only these children were vaccinated (as children with two scars and those absent when the team visited were not vaccinated). Selecting the population for analysis on the basis of the BCG scar reading permits the identification of a comparable subpopulation in schools allocated to the control group. Children without a BCG scar reading correspond to 26% of the children in the database and those with two, more or doubtful BCG scars to 7.4% of the children with a scar reading. As incidence of tuberculosis will be calculated for the children without a scar reading, it is possible to test whether they were comparable in vaccination and control schools. The data management team recommended undertaking a final analysis rather than interim analysis as there was no need to monitor safety since recruitment and vaccination lasted only a short period.

Ethical and political issues

Ethical issues

Two ethical committees approved the trial: University Hospital, Universidade Federal da Bahia, Brazil, and London School of Hygiene and Tropical Medicine, London University, UK. The main ethical issue discussed was the trial not including a signed informed consent from participants. A second dose of BCG vaccination was the current recommendation by

the Ministry of Health and it had been implemented in some states, whereas not receiving the intervention was the routine in most states in Brazil. Since both the intervention and the absence of that intervention were in routine practice in the country, the study team and the ethical committees that considered the study were satisfied that informed consent was not required. Parents of children in schools allocated to vaccination were given information about the trial, the vaccine and adverse events in an information pack, and they were offered the opportunity to withdraw their child from the trial. Parents were also offered a meeting at the school to discus the study with the study team. Parents in very few schools took up this offer.

Building consensus

The study team considered that on ethical and political grounds, it was important to seek support from the medical community and organizations in charge of health and education in Brazil. The study was conceived as a response to the recommendation of BCG revaccination, and the Ministry of Health was a strong supporter and a main sponsor of the project. The support of the local health and education authorities was essential for the involvement of professionals in both sectors and to encourage the school children to participate in the study. The support from medical societies (of chest physicians and pediatricians) was vital to involve the medical community; the society support was expected to result in an increase of advice to participate in the study given to parents asking for expert opinion.

Baseline characteristics

The children in the database

The process of selection leading to the final study population is presented in Fig. 1. There are 763 schools in the study with 351,951 children in the study database. Fifty-one percent of the schools (388) are in the intervention group, with 50.7% of the children (178,513). There is variation in the number of children in each school, ranging from 2069 to 37 children. The mean number of children in schools allocated to vaccination is 460 and in unvaccinated schools 462. The mean age of children in schools allocated to vaccination is 10.8 years (standard deviation [S.D.]=2.2) and in control schools 10.9 (S.D.=2.2); the male/female ratio is 0.978 in schools allocated to vaccination and 0.980 in control schools. A total of 261,714 (74.4%) children had a scar reading. This proportion is similar in schools allocated to vaccination (76.2%) and to control (72.5%).

Children absent from school

We compare the incidence of tuberculosis in children who were not present when the study team visited (those without a scar reading) in schools allocated to vaccination and in control schools, as cases in these children are ascertained and validated using study procedures. The incidence so far in these children allocated to vaccination and to the control group is respectively 24 (95% CI 16–34) cases per 100,000 person years and 25 (95%CI 18–35) cases per 100,000 person years.

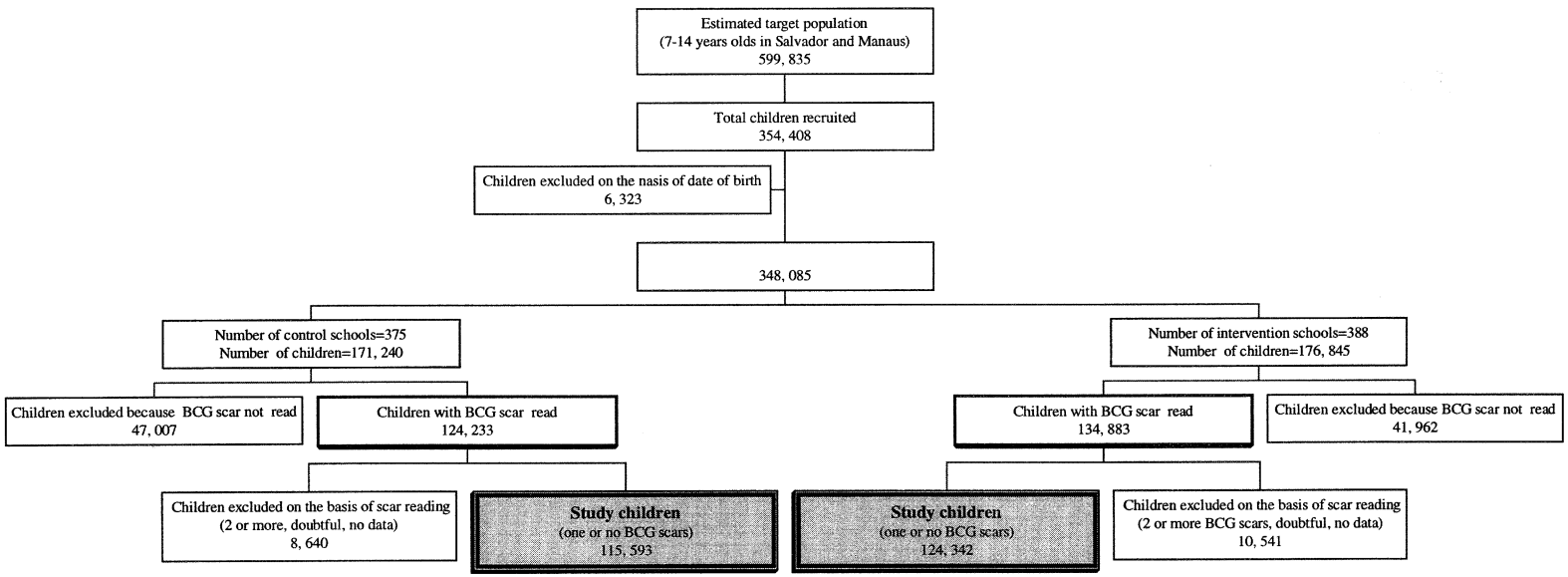

Fig. 1. Participant flow diagram.

The study children

There are 242,401 study children (those with no or one previous BCG scar) to include in the analysis, of whom 125,403 (51.7%) attended schools allocated to vaccination [18]. The mean age of study children in schools allocated to vaccination is 10.8 years (S.D.=2.1) and in control schools 10.9 (S.D.=2.1); the male/female ratio is 0.932 in schools allocated to vaccination and 0.940 in control schools. The proportion of study children with one scar is 83.4% in schools allocated to vaccination and 83.9% in unvaccinated schools.

The linkage process

Of the first 518 cases ascertained, 201 (39%) were linked and 317 were unlinked. We undertook a validation study of the first 218 unlinked cases in Salvador by visiting them at home and establishing whether they were truly not in the study database or were failures of linkage. The residence of 34% was not found, either because the address given did not exist, or because it was not specific enough. This compares with 28% in 68 cases linked to the study database who were visited to collect information for the case validation study. Of the remaining 144 unlinked cases whose residence was found, 143 were found not to belong to the study population: about 29% did not live in Salvador or were outside the target age group; 44% were registered in schools not in the study (half of which were private schools); 14% were not registered in a school at all. Thirteen percent were reported to be enrolled in trial schools, but their names could not be found in the school lists at all or only outside the study period. Only 1 of 144 unlinked cases interviewed was shown to be a failure of linkage: the linkage failed because the stepmother gave her name as the mother at the tuberculosis control program but not at the school (where the birth certificate must be presented at registration). The results of this exercise suggest that linkage is working extremely well.

Discussion

The present trial was designed to provide evidence to inform a policy decision that had been taken on the basis of limited scientific knowledge. It aimed to be a large, simple trial to estimate the effectiveness of the BCG vaccine and the level of protection that the intervention would offer if implemented.

The implementation of the study so far indicates that these aims were achieved and that the proposed design is feasible. The randomization resulted in comparable intervention and control groups. The intervention was delivered as it would be in routine conditions. This uncovered the fact that one third of the children registered in state schools would be missed by a routine vaccination schedule that visited schools only once, and that a proportion of cases of tuberculosis are likely to be outside the state school system. Should the recommendation be maintained after the trial, the vaccination strategy needs to be examined to incorporate these findings.

The study does not use a placebo and, because it relies on diagnosis by the routine system, does not enable blindness by diagnosing physician. How could this lack of blindness bias the study? Presence of a second BCG scar could lead to underdiagnosis by a physician who believed in BCG protection. In a very medicalized society like urban Brazil, it is unlikely that a

case of tuberculosis would remain undiagnosed, so we do not expect underdiagnosis of vaccinated cases. Another possible bias introduced by lack of blindness would be a positive PPD test (more common in vaccinated children) leading a physician to diagnose tuberculosis in a borderline case. Case validation is done independently and blind to exposure and to PPD test results by two study chest physicians so the possibility of bias is limited. Any bias in this case would tend to decrease any protective effect of BCG.

The follow-up relies on the existing structures to a large degree. Because follow-up is passive, we do not have the ability to identify losses. These would occur either by death, migration outside the area, or change of name (for example by marriage), disrupting the linkage. Losses to follow-up are of concern only if biased in relation to exposure. The intervention (BCG vaccination) is unlikely to be associated with migration, death or change of name, and therefore losses will decrease the power of the study but are unlikely to cause imbalance between vaccinated and control groups.

We expect the study to provide an accurate measure of the effect that BCG vaccination of school children would have in the intended population, the measure needed to inform health policy decisions [15]. An additional advantage of this design is that follow-up could continue for years after the primary outcome is studied to estimate the effect on specific forms of tuberculosis on specific subgroups of the population (including those living in a region with low or high prevalence of mycobacteria) and whether there is waning with time of any observed protection.

This trial also shows that important policy and scientific questions can be answered very efficiently if there is good collaboration between those in charge of implementing health policies and those in academia. It is also an example of the type of alternative strategies that would be needed to evaluate the increasing number of vaccines and other preventive technologies currently being developed. This is particularly important in developing countries as the high cost of evaluation can be used as an argument for adopting new complex interventions tested elsewhere without adequate investigation of their effects and cost in a specific developing country context.

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