INTERNATIONAL JOURNAL OF LEPROSY

Volume 72, Number 1
Printed in the U.S.A.
(ISSN 0148-916X)

Design of the Leprosy Component of the Brazilian BCG Revaccination Trial for Assessing BCG Effectiveness against Leprosy in School Children[1]

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ABSTRACT

Background. BCG vaccination confers protection against leprosy, and vaccination among household contacts has been recommended in Brazil. Nevertheless, vaccination of the entire community against leprosy is not advocated as leprosy has low incidence in most populations. Despite that, in Brazil, BCG vaccination is recommended among school children to prevent tuberculosis and this large scale vaccination may also affect the occurrence of leprosy, which led to investigations of its impact on leprosy in endemic areas of Brazil.

Objectives. To estimate the effectiveness against leprosy of a dose of BCG vaccine given to school children in a population with a high coverage of neonatal BCG. Long term objectives are to compare the impact of vaccination among schoolchildren with the existing recommendation to vaccinate household contacts of leprosy.

Study design. Cluster randomized controlled field trial with no placebo.

Study population. Children aged 7 to 14 years attending state schools with high coverage of neonatal BCG.

Methods. 286 state schools in the city of Manaus, Brazil, were randomized to receive BCG or not. Identifying information was collected for 152,438 school children, of whom 72,980 are in intervention schools. BCG vaccination was given intradermically to children in schools allocated to vaccination. Follow-up relies on ascertainement of cases diagnosed at the health services and notified to the reference center for leprosy.

RÉSUMÉ

Background. La vaccination par le BCG confère une protection contre la lèpre, et la vaccination des contacts vivant sous le même toit a été recommandée au Brésil. Cependant, la vaccination de tous les membres d'une communauté contre la lèpre n'est pas encouragée parce que la lèpre présente une incidence faible dans la plupart des populations. Malgré cela, la vaccination par le BCG est recommandée au Brésil pour les enfant en âge d'aller à l'école pour la prévention de la tuberculose et cette vaccination à grande échelle pourrait aussi influencer l'incidence de la lèpre, ce qui nous a amené à explorer son impact éventuel sur la lèpre dans les régions endémiques du Brésil.

Objectifs. Estimer l'efficacité contre la lèpre d'une dose de vaccin BCG administré à des enfants scolarisés dans une population présentant une forte couverture de vaccination au BCG à la naissance. Les objectifs à long terme sont de comparer l'impact de la vaccination

[1] Received for publication 7 November 2002. Accepted for publication 1 December 2003.

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parmi les enfants scolarisés avec la recommandation existante de vacciner les personnes en contact avec un lépreux et vivant sous le même toit.

Plan d'étude. Essai clinique de terrain avec témoins, sans placebo, répartis par groupes.

Population d'étude. Enfants de 7 à 14 ans scolarisés dans les écoles publiques, présentant une couverture importante de BCG administrés à la naissance.

Méthodes. 286 écoles d'état de la ville de Manaus, au Brésil, furent assignées au hasard pour recevoir ou non le BCG. Des informations d'état civil furent collectées chez 152 438 écoliers, parmi lesquels 72 980 sont dans des écoles d'éducation prioritaire. Un vaccin BCG fut administré en intra-dermique aux enfants scolarisés dans les établissements désignés pour la vaccination. Le suivi repose sur les cas diagnostiqués par les services de santé et sur les déclarations au centre de référence de la lèpre.

RESUMEN

Panorama. La vacunación con BCG confiere protección contra la lepra, y en Brasil se recomienda la aplicación de esta vacuna entre los contactos convivientes de los pacientes con lepra. Sin embargo la vacuna BCG no se aplica a la comunidad entera debido a que la lepra tiene una baja incidencia en la mayoría de las poblaciones. Por otro lado, la vacunación con BCG se aplica rutinariamente entre los niños escolares en Brasil, como prevención contra la tuberculosis. Suponemos que la vacunación en gran escala con BCG podría también incidir sobre la ocurrencia de lepra, y esto hace necesario el estudio sobre su impacto en la lepra, en las áreas endémicas de Brasil.

Objetivos. Calcular la efectividad contra la lepra de una dosis de vacuna BCG aplicada a niños escolares en una población con una alta cobertura de BCG neonatal. Un objetivo a largo plazo es la comparación del impacto de la vacunación entre los niños escolares con la recomendación existente de vacunar a los contactos convivientes de los pacientes con lepra.

Diseño del estudio. Estudio de campo aleatorio controlado sin placebo.

Población de estudio. Niños de 7 a 14 años, alumnos de escuelas estatales con alta cobertura de BCG neonatal.

Métodos. Participaron 286 escuelas estatales de la ciudad de Manaus, Brasil y la mitad de ellas se asignó, aleatoriamente, para aplicar o no la vacuna BCG. Se colectó la información de identificación de 152,438 niños escolares, de los cuales 72,980 pertenecían a escuelas de intervención. La vacuna BCG se administró intradérmicamente en los niños escolares de las escuelas seleccionadas. El seguimiento se basa en el registro de los casos diagnosticados en los Servicios de Salud notificados al Centro de Referencia de la Lepra.

It is well established that a single dose of BCG confers protection against leprosy, with estimates ranging from 20% to 90% efficacy in different studies ([8, 12]), and multiple doses of BCG appear to confer additional protection ([3, 5, 11]) (although this finding has not achieved statistical significance in the study in Venezuela) ([5]). However, as leprosy has low incidence in most populations, the number of individuals needed to be vaccinated to prevent one case of leprosy tends to be large ([20]) unless applied in high risk groups. Therefore, the Ministry of Health in Brazil recommends vaccination only among household contacts of leprosy cases ([16]).

Brazil has had a high coverage of neonatal BCG since the 1980's. In 1994 the Brazilian Ministry of Health recommended the routine application of BCG among school children to prevent tuberculosis ([17]), and a trial (BCG-REVAC) was proposed to assess the effectiveness of the recommended measure. This trial is being conducted in two cites, Salvador and Manaus ([2]). Brazil, with a population of nearly 170 million, has the second largest number of leprosy cases in the world ([23]).

Vaccine efficacy trials aim to estimate the protection under ideal conditions ([4]), and are standard for vaccine licensure by regulatory agencies. However, the results of such studies do not correspond to the protection given by the vaccine in the target population under routine conditions. The effect under routine conditions [vaccine effectiveness (VE)] has been traditionally estimated through observational studies, and these studies are more vulnerable to bias than trials. The effectiveness trial concept was proposed to incorporate the randomization process and elements of a public intervention implementation approximating routine conditions. Effectiveness trials attempt

to reproduce real conditions. The BCG-REVAC trial was planned as a vaccine effectiveness trial, and its study design attempts to reproduce the routine implementation of a BCG vaccination policy to school children according to the 1994 recommendation. Manaus, one of the trial sites, is an endemic area of leprosy. This trial created the opportunity to estimate the impact of the recommended BCG vaccination among school children on the occurrence of leprosy. We therefore expanded the objectives of the trial in the city of Manaus—where the recommendation to vaccinate contacts has not been completely implemented so far—to include the estimation of protection of BCG against leprosy.

The objective of this paper is to describe the rationale, study design, implementation and proposed analysis of the leprosy component of the trial. The design of the trial component for preventing tuberculosis has been published elsewhere ([2]).

DESIGN AND METHODS

The main objective of the leprosy component of the trial is to estimate the protection against all forms of leprosy of one dose of BCG given under routine conditions. Long-term objectives are to estimate effectiveness by age and clinical form, and to compare this policy with the existing recommendation to vaccinate household contacts of leprosy, in terms of impact on occurrence of leprosy and in term of costs. This text will only describe the main objective.

Study site. Manaus is an urban center on the banks of the Negro River, Amazonas State, in Brazil, with about 1,500,000 inhabitants in 2002. The annual new case detection rate (NCDR) of leprosy has been stable at around 6.0 per 10,000 inhabitants in the 1990's. In 1997 it was 6.6 (814 cases) in the total population and 4.9 (110 cases) in children aged 7 to 14 yrs. Sixty percent of all cases detected in 1996 were classified as tuberculoid or indeterminate and 40% as multibacillary.

Study population. The target population consisted of school children residing in Manaus, as that covered by the 1994 recommendation for BCG vaccination against tuberculosis, and restricted to those aged 7 to 14 yrs and attending state schools at the time of the trial implementation (born between 1984 and 1991). Only schools with more than 50 pupils in this age group were included in this study.

This population has a high coverage of neonatal BCG: official data reported coverage rate of 56.8%, 74.8%, 82.0%, 89.0%, for those born in 1988, 1989, 1990, and 1991, respectively. Therefore, for most people this will be a second dose. No child was excluded on the basis of previous history of tuberculosis or leprosy.

Screening for detecting leprosy and HIV infection. An increase in the risk of leprosy has been described in the initial follow-up period in some trials ([10, 13]) (but not reported in all of them). However, this trial did not include screening for leprosy before vaccination. This was for two reasons. First, the trial aims to estimate the vaccine effectiveness under the recommended policy for tuberculosis and this policy does not include previous screening ([17]), even though Brazilian policy for BCG vaccination among household contact of leprosy includes screening for detecting leprosy before vaccination. Such a screening among school children as a requirement to vaccination would probably not be feasible because of the large number of individuals, and would be a time-consuming operation. Secondly, the increase in risk for leprosy, if present, was expected to be transient and would not be considered an obstacle to a BCG large-scale vaccination in leprosy endemic areas.

Although BCG vaccination carries a risk of severe adverse effects when given to people with AIDS ([22]), screening for HIV infection was not done. The prevalence of AIDS in Manaus and in this age group is low (one case was reported during the whole period of 1998 to 2001 among those aged 7 to 14 yrs) ([15]), and the 1994 recommendation for BCG among school children does not require HIV screening.

Outcomes. All leprosy cases from Manaus reported by the local surveillance service and belonging to the target population have been recorded. The incidence of leprosy is expressed as the NCDR of leprosy per 10,000 person years in the two comparison groups during the trial follow-up.

Sample sizes and follow-up period. Leprosy has a long incubation period ([7]) but the protective effect of BCG against leprosy was observed very soon in some trials ([1, 21]).

As most cases in Manaus are paucibacillary, with a shorter incubation period ([7]), the sample size was chosen to allow a first intermediate analysis after 4 to 5 yrs of follow-up. The study power at this phase would not necessarily be sufficient for detection of differences in VE between clinical forms or previous vaccination status. To estimate the sample size for the leprosy component of the trial, we used the formula described in chapter 7 in Friedman, *et al.* ([9]):

$$2N = 2\left[Z\alpha\sqrt{2\bar{P}(1-\bar{P})} + Z\beta\sqrt{Pc(1-Pc) + Pi(1-Pi)}\right]^2 / (Pc - Pi)^2$$

Where Pc and Pi are the incidence proportions in control and intervention groups, respectively; $P = (Pc + Pi)/2$, $Z\alpha$ is the critical value corresponding to the significance level α type I error; $Z\beta$ corresponds to the power. The following parameters were used to estimate the sample size:

- study power of 80% and 90%;
- type I error of 5%;
- VE of 50% [as observed in the Malawi trial ([11])];
- NCDR of 4 per 10,000 per year in the control group (overall NCDR in this age group in Manaus),
- and assuming that rate is constant with age over time.

This resulted in estimates for different follow-up periods and study power, presented in The Table. Finally, it was agreed on a sample size of 50,000 individuals in each arm. This number was below the sample size of the original tuberculosis trial for the city of Manaus ([2]). Leprosy cases reported before the trial started, but who would have met the trial entry criteria, were used to estimate the intra-class correlation (ICC) and the design effect (DEF) of the NCDR of leprosy. The ICC was estimated taking schools as clusters. ICC and DEF were estimated as –0.00088 and 0.95, respectively, and thus the sample size was not inflated.

Randomization. Schools (N = 286) were the randomization unit and were firstly allocated to strata defined on the basis of number of students registered in 1996 in the age group, and incidence of leprosy and tuberculosis in 1996 in the geographical areas where schools were located. The city of Manaus is divided in 56 administrative areas (districts) that are grouped into 6 greater geographical areas (South, North, West, East, Center-West, Center-South). These 56 districts were categorized into those with incidence of leprosy (NCDR) below or above to the incidence of the city as a whole. The same procedure was used for tuberculosis. The districts were then classified into five levels: four combinations of incidence of tuberculosis and leprosy, and a fifth category of the districts with unreliable or unavailable data on tuberculosis or leprosy. The 286 schools were then sorted by geographical areas, number of students and incidence of leprosy and tuberculosis, and paired. One school in each pair was allocated at random to the control group—the other was allocated to the intervention group. When a school had no pair (odd number of schools in the stratum), this last school was allocated at random.

THE TABLE. *Size in each arm needed for an observed vaccine effectiveness of 50% in Manaus and for study power of 80% and 90%.*

Year of follow-up	Cumulative incidence (%)[a]	Study power	
		80%	90%
1st	0.04	117,563	157,610
2nd	0.08	58,764	78,780
3rd	0.12	39,164	52,503
4th	0.16	29,364	39,365

[a] Baseline incidence estimated in 4 per 10,000 a year (0.04%).

Implementation. *Trial coordination.* Overall co-ordination of the trial is from the Instituto de Saúde Coletiva (Brazil) and London School of Hygiene and Tropical Medicine (U.K.). Collaborating centers are: Fundação Alfredo da Matta (FUAM), Brazilian National Health Foundation and Brazilian National Immunisation Programme. The planning and co-ordinating research team for Manaus included the local co-ordinators and most members of the team of the second study site of the tuberculosis component (Salvador). There were two local co-ordinators: a clerk with experience in implementing surveys was responsible for the recruitment and data collection, and a nurse with experience in managing surveillance and BCG vaccination was re-

sponsible for vaccination and surveillance for adverse effects. Professionals from the local leprosy reference service (Fundação Alfredo da Matta, FUAM) are involved in the ascertainment and validation of leprosy cases.

Recruitment, vaccine ascertainment, and vaccination. In the recruitment phase, field workers transcribed data (full name, date of birth, sex, full name of the mother, address) from school records to a standard form. This was done without contact with the students. Afterwards, BCG scar was read to ascertain neonatal vaccination status ([2]).

Vaccination (0.1 ml) was done by trained nurses through intradermal injection in the deltoid region of the right arm. The lyophilized BCG used in Brazil contains the Moreau strain, related to the Japanese and Russian strains ([6]). This is the vaccine used by the Brazilian National Immunization Program (PNI), and has been shown to offer high protection against leprosy in Brazil ([12, 14, 19]). Four different batches were used in Manaus and vaccination in each school was done with a single batch. The vaccines were stored at the local immunization program and delivered to the campaign headquarters when required. The vaccines were kept refrigerated and the temperature checked regularly using the routine cold chain facilities.

Surveillance of adverse events. The routine passive surveillance for adverse events was enhanced. A letter containing information on BCG adverse events was distributed to all children on the day of vaccination to motivate parents to take children to a health facility if they had a health problem following vaccination. Health workers in the reference medical centers for tuberculosis and leprosy were made aware of the trial and alerted to possible BCG adverse events. Suspected adverse events were expected to be diagnosed in the health facilities and treatments for adverse events provided. This vaccine safety surveillance continued for 4 months after the end of vaccination.

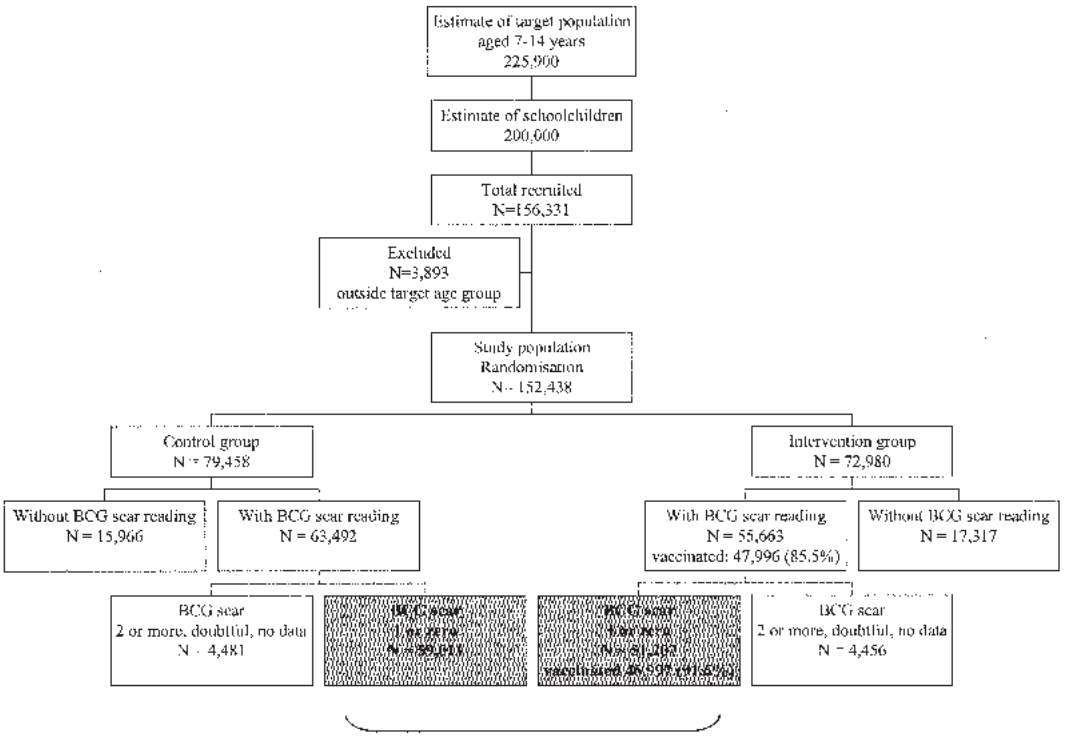
Avoidance of bias. This study is not a double-blind trial and there was no concealment of allocation, so study participants knew whether they received the vaccine, which could lead to detection bias. However, bias is not expected as those with clinical features of leprosy are equally likely to seek medical attention irrespective of vaccination status. Linkage of leprosy cases to the study population is done blind to vaccine status, and physicians are not aware about the BCG status of the most leprosy cases (see below).

Another potential source of contamination is vaccination in individuals allocated to the control group after the start of the trial due to vaccination among household contacts of leprosy cases, leading to an underestimate of the vaccine effectiveness. However, this vaccination in contacts is scarcely implemented in Manaus (in 1998, official data reported 60 individuals for all age groups who received BCG to prevent leprosy) ([15]) and the managers of the local immunization program agreed in not enhancing this vaccination among contacts before the first phase of the trial.

Follow-up procedures. *Passive follow-up and case ascertainment.* Follow-up consists of identifying cases in the surveillance system and establishing whether they are from the trial population through linkage. Although several health facilities undertake leprosy diagnosis in Manaus, 70% of all cases are diagnosed and treated in the local leprosy reference center (FUAM), where the state epidemiological surveillance service for leprosy is based. All leprosy cases in FUAM are submitted to biopsy and skin smear. A standardized notification form is routinely completed for all leprosy cases in the other diagnosing units and forwarded to FUAM where data are entered into a computerized database, so data from all leprosy cases can be easily obtained.

Physicians are asked to refrain from inquiring about the BCG status until a definitive diagnosis is made, unless the physician judges it necessary to know the BCG status for good clinical practice. A standard form was developed in the local reference center (FUAM) to collect information on whether the clinician was aware of the BCG vaccination status of the patient. Cases are routinely categorized according to the criteria adopted by the Brazilian Ministry of Health (based on the Madrid Conference and two groups system proposed by the World Health Organization) ([16]), and based on Ridley-Jopling classification ([18]).

Setting up the database and linkage of cases. The study has two databases. The data on the recruited study population were



THE FIGURE. Flowchart of the study participants in the city of Manaus eligible to receive the vaccine. The vaccine effectiveness will be estimated by comparing the incidence rates between control (59,011) and intervention (51,207) groups.

entered in the first database (study population database). It contains identification data (which were transcribed from school records to a standardized form during the recruitment phase), neonatal BCG vaccination (mainly from BCG scar reading) and vaccination by the trial. Clinical and laboratory data for each case of leprosy detected during the follow-up, as recorded in the reference center and by the surveillance services, are entered in a second database (case database). Records in the case database are matched to the records in the study population database, based on variables present in both databases: subject's name, date of birth, sex, and mother's name, without access to data on whether the study participants had received BCG. This matching is done twice by two independent researchers.

Concerns. This trial as a whole is a joint collaboration involving the two academic institutions and the Brazilian Ministry of Health. Two ethical committees (Universidade Federal da Bahia, Brazil; and London School of Hygiene and Tropical Medicine, U.K.) approved the original trial of tuberculosis. The leprosy component trial was added to the trial of tuberculosis later. The initial view was that ethical approval was not required because the main additional activity was the ascertainment of leprosy cases from routine sources. This was revised later on, and the trial received ethical committee approval by the National Ethical Committee in 2003.

RESULTS

Field work (recruitment) in Manaus began in July and finished in December 1998. Vaccination began in September and finished in December 1998. The starting point for the follow-up of new leprosy cases was on 1 January 1999.

The Figure shows the population as enrolled in the study and the sub-populations to be used in the estimate of the VE. Records were collected in 286 schools (140 schools in intervention group and 146 in

control group). Information on identification was collected on 156,331 individuals, corresponding to about 69.0% of the population of Manaus in this age group. From this group, 3893 individuals were excluded because they were outside the target age group and thus 152,438 individuals remained: 79,458 in schools allocated to the control arm and 72,980 in schools allocated to vaccination. The proportion of individuals with a BCG scar reading was similar in control and intervention groups (79.9% *vs* 76.3%, respectively). The groups in which the VE will be estimated are constituted of 110,218 individuals with either no BCG scar or one BCG scar. Among those 51,207 in the intervention group, 46,997 were vaccinated and 4210 were not due to the following reasons: 11 had already two BCG doses reported in vaccination cards or by the guardians, 843 refusals by the school children, 2342 refusals by their guardians, 68 were not present at the moment of vaccination, 946 for reasons not documented.

DISCUSSION

VE will be estimated by comparing the incidence of leprosy among individuals in the original allocation groups, but including only those with BCG scar reading and of these, only those with no scar or one BCG scar (N = 110,218). The first analysis will be done when the total number of leprosy patients in this group allows a study power above of 80% for a vaccine effectiveness of 50%. This analysis consists of an intention-to-treat approach in which 92% (46,997) of the individuals allocated to vaccination were vaccinated. So, a vaccine effectiveness of 50% will be observed as 46%, which does not represent a significant loss of power.

The proposed plan of analysis for the main objective will mainly consist of three phases. First, the description of the baseline characteristics of the study population. Second, the effect of cluster will be estimated. Third, estimation of the VE will be obtained as the percent reduction in NCDR per person-year among unvaccinated individuals as compared to those vaccinated. The VE will be estimated for the total number of leprosy cases and separately for time period from vaccination, age group, sex, neonatal BCG vaccination and clinical forms. The estimation of VE will be estimated by standard statistical procedures and also adjusted by the effect of clustering.

Acknowledgment. The trial is supported by grants from the Department of International Development, U.K. (DFID) and the National Health Foundation, Brazil (Fundação Nacional de Saúde). The first author (S. S. Cunha) received support from Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brasilia-Brazil. We thank the health and the education departments for the State of Amazonas, the Brazilian National Immunization Program and the National Center for Epidemiology in Brazil, in special Dr. Maria de Lourdes Maia. We thank Edna Ackerman, Ivanise Cunha, and the field workers in the vaccination and data collection teams. Ms. Meguni Sadahiro, Dr. Antonio Schetini and Dr. Maria da Graça Cunha (Fundação Alfredo da Matta), and Dr. Simon Cousens (London School of Hygiene and Tropical Medicine, U.K.), for their work as scientific advisors. Dr. Gerson O. Penna (Núcleo de Medicina Tropical, Universidade de Brasília, Brazil) for his comments on early draft. Ms. Silvana de Castro de Brito (Instituto de Saúde Coletiva) for her work in the case linkage. Mr. José Carlos and Ms. Fátima Praia for co-ordinating the field work.

Contributions. All authors fulfilled the criteria for authorship proposed by Vancouver Conference: concept of the study, drafting the article or revising it critically for important intellectual content and all had the final approval for its content. S. C. Cunha, L. C. Rodrigues, and M. L. Barreto had the primary responsibility for epidemiological study design. E. S. Pereira, M. F. Maroja, and C. Ribas (Fundação Alfredo da Matta) are engaged in the case detection. Mr. José Carlos and Ms. Fátima Praia were primarily responsible for the recruitment and vaccination.

REFERENCES

1. Bagshawe, A., Scott, G. C., Russell, D. A., Wigley, S. C., Merianos, A., and Berry, G. BCG vaccination in leprosy: final results of the trial in Karimui, Papua New Guinea, 1963–1979. Bull. World Health Organ. **67(4)** (1989) 389–399.
2. Barreto, M. L., Rodrigues, L. C., Cunha, S. S., Pereira, S. M., Hijjar, M. A., Ichihara, M. Y., de Brito, S. C., and Dourado, I. Design of the Brazilian BCG-REVAC trial against tuberculosis: a large, simple randomised community trial to evaluate the impact on tuberculosis of BCG revaccination at school age. Control Clin. Trials **23** (2002) 540–553.
3. Bertolli, J., Pangi, C., Frerichs, R., and Halloran, M. E. A case-control study of the effectiveness of BCG vaccine for preventing leprosy in Yangon, Myanmar. Int. J. Epidemiol. **26(4)** (1997) 888–896.

4. Clemens, J., Brenner, R., Menng, M., Tafari, N., and Lowe, C. Evaluating new vaccines for developing countries. Efficacy or effectiveness? JAMA **275** (1996) 390–397.
5. Convit, J., Smith, P. G., Zuniga, M., Sampson, C., Ulrich, M., Plata, J. A., Silva, J., Molina, J., and Salgado, A. BCG vaccination protects against leprosy in Venezuela: a case-control study. Int. J. Lepr. Other Mycobact. Dis. **61(2)** (1993) 185–191.
6. Desmond, M., Collins, M., and de Lisle, G. W. BCG identification by DNA restriction fragment patterns. J. Gen. Microbiol. **133** (1987) 1431–1434.
7. Fine, P. E. Leprosy: the epidemiology of a slow bacterium. Epidemiol. Rev. **4** (1982) 161–188.
8. Fine, P. E. Primary prevention of leprosy. Int. J. Lepr. Other Mycobact. Dis. **64(suppl. 4)** (1996) S44–S49.
9. Fleiss, J. *Statistical Methods for Rates and Proportions*. New York: John Wiley & Sons, 1973.
10. Gupte, M. D., Vallishayee, R. S., Anantharaman, D. S., Nagaraju, B., Sreevatsa, Balasubramanyam, S., de Britto, R. L., Elango, N., Uthayakumaran, N., Mahalingam, V. N., Lourdusamy, G., Ramalingam, A., Kannan, S., and Arokiasamy, J. Comparative leprosy vaccine trial in south India. Indian J. Lepr. **70(4)** (1998) 369–388.
11. Karonga Prevention Trial Group. Randomized controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. Lancet **348(9019)** (1996) 17–24.
12. Lombardi, C., Pedrazzani, E. S., Pedrazzani, J. C., Filho, P. F., and Zicker, F. Protective efficacy of BCG against leprosy in São Paulo. Bull. Pan. Am. Health Organ. **30(1)** (1996) 24–30.
13. Lwin, K., Sundaresan, T., Gyi, M. M., Bechelli, L. M., Tamondong, C., Garbajosa, P. G., Sansarricq, H., and Noordeen, S. K. BCG vaccination of children against leprosy: fourteen-year findings of the trial in Burma. Bull. World Health Organ. **63(6)** (1985) 1069–1078.
14. Matos, H., Duppre, N., Alvin, M., Vieira, L., Sarno, E., and Struchiner, C. Epidemiologia da hanseníase em coorte de contatos intradomiciliares no Rio de Janeiro (1987–1991). Cad Saúde Pública **15** (1999) 533–542.
15. Ministério da Saúde. DATASUS. Available from: http://www.datasus.gov.br. Accessed on 20 September 2003.
16. Ministério da Saúde. Hanseníase. Vigilância Epidemiológica de Doenças e Agravos Específicos. Available from http://www.funasa.gov.br/pub/GVE/GVE0513A.htm. Accessed on 20 July 2003.
17. Ministério da Saúde. Segundo informe técnico sobre a vacinação e revacinação BCG. Brasilia, 1994.
18. Ridley, D. S., and Jopling, W. H. Classification of leprosy according to immunity. A five-group system. Int. J. Lepr. **34** (1966) 255–273.
19. Rodrigues, M. L., Silva, S. A., Neto, J. C., de Andrade, A. L., Martelli, C. M., and Zicker, F. Protective effect of intradermal BCG against leprosy; a case-control study in central Brazil. Int. J. Lepr. Other Mycobact. Dis. **60(3)** (1992) 335–339.
20. Smith, W. C., and Smith, C. M. Preventive treatment of leprosy: needs, opportunities, and feasibility. Int. J. Lepr. Other Mycobact. Dis. **67(suppl. 4)** (1999) S38–S44.
21. Stanley, S. J., Howland, C., Stone, M. M., and Sutherland, I. BCG vaccination of children against leprosy in Uganda: final results. J. Hyg. Lond. **87(2)** (1981) 233–248.
22. Talbot, E. A., Perkins, M. D., Silva, S. F., and Frothingham, R. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. Clin. Infect. Dis. **24** (1997) 1139–1146.
23. World Health Organization. Leprosy—global situation. Weekly Epidemiol. Rec. **75** (2000) 226–231.