Effectiveness of BCG vaccination against tuberculous meningitis: a case–control study in São Paulo, Brazil

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A case–control study was carried out in the Metropolitan Region of São Paulo, Brazil, to determine the protection against tuberculous meningitis conferred by BCG vaccination to children aged less than 5 years. The BCG vaccination coverage in the study area was about 88%. A total of 72 tuberculous meningitis patients were studied as well as 505 neighbourhood and 81 hospital controls. Analysis of the data using a conditional logistic regression for matched case–control studies indicated that the efficacy of BCG was similar for both groups of controls, that for neighbourhood controls (84.5%) being slightly greater than that for hospital controls (80.2%). No significant interactions were found between vaccination status and sex, age, or socioeconomic status.

Introduction

At the beginning of the last decade of the 20th century, tuberculosis still presents a public health challenge, particularly in developing countries. In Brazil the death rate from tuberculosis has dropped systematically since the introduction of specific chemotherapy. However, the current death rate of 5.9 per 100 000 per year from tuberculosis indicates that, apart from intestinal infections and pneumonia, it is still the infectious disease that causes most deaths in the country (14). According to official figures, the incidence of tuberculosis has shown a tendency to rise in Brazil (11). The annual risk of infection is, however, not precisely known because the policy of mass and indiscriminate vaccination with BCG has not facilitated such estimates.

To reduce the global problem of tuberculosis, international health bodies have designated the identification and treatment of cases and vaccination with BCG as the principal components of control programmes (25). Intradermal injection of BCG is considered to be the best method of immunizing against the disease. Nevertheless, the effectiveness of BCG has been placed under doubt since several controlled trials reported contradictory results, with efficacies

that ranged from zero to 76% (2–5, 7–9, 12, 17, 18, 24). More recently, the case–control approach has been advocated for the evaluation of the effectiveness of BCG vaccination (21, 22); however, such studies have also reported a wide range of efficacies (13, 19, 23).

Notwithstanding doubts about the effectiveness of BCG on the chain of transmission of tuberculosis, and therefore on the incidence of and death rate from the disease, the vaccine may still be useful if it gives protection against severe infantile forms of tuberculosis, although such forms are not contagious (1, 15, 16). The results of a study in the United Kingdom in 1950 already indicated that BCG vaccine offered such protection (4); however, the results of a survey conducted in Chingleput, India, were unclear on this matter (1, 12).

In Brazil, tuberculous meningitis is a notifiable disease. For all cases of the disease a surveillance form is completed, covering data from clinical and laboratory examinations and an epidemiological history (6). Despite the difficulties in diagnosing this type of tuberculosis and the lack of confidence in the data collection in countries with socioeconomic characteristics such as Brazil, the seriousness of the disease probably results in all cases being notified.

The hypothesis that BCG offers greater protection against tuberculous meningitis than against pulmonary tuberculosis (4) is consistent with evidence from two Brazilian states with different schedules for BCG vaccination. For example, in Rio Grande do Sul, where children aged 7 years or older are vaccinated with BCG, the incidence of pulmonary tuberculosis in 1982 was about 12.5 times greater than that of tuberculous meningitis. In contrast, in São Paulo, where children receive BCG vaccine during the first year of life, the incidence of pulmonary

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tuberculosis to that of tuberculous meningitis was
52:1; regional differences may, however, confound
this apparent relationship.

BCG vaccine coverage varies markedly in dif-
ferent regions of Brazil. Vaccine coverage in São
Paulo city is reported to be very high, exceeding
100% according to official estimates; a survey con-
ducted in 1982–3, however, estimated that the
coverage was 88% for children less than 18 months
of age.[a]

In view of these facts and of the necessity to
better define the role of BCG in tuberculosis control
programmes, we carried out a case–control study in
the Metropolitan Region of São Paulo to evaluate
the effectiveness of BCG against tuberculous menin-
gitis. Our findings are reported here.

Materials and methods

Study area

The study was conducted in the Metropolitan Region
of São Paulo (MRSP), which comprises 37 muni-
cipalities within an area of 8053 km[2]. The population
of MRSP recorded in the 1980 census was 12.5
million, which corresponded to 50.3% of that of the
State of São Paulo and 10.6% of the entire Brazilian
population. A wide range of living standards prevail
in the study region, with some areas having only very
basic environmental and social amenities. MRSP is
very urbanized with only a few rural areas in the
outskirts of the city (20).[b]

Tuberculous meningitis

Between 1979 and 1983, about 150 cases of tuber-
culous meningitis per annum were notified in the
State of São Paulo, and of these a third were among
children under 5 years of age (incidence, approx-
imately 1.7 per 100 000 per annum). The majority of
cases of the disease notified in the State of São Paulo
are admitted to two hospitals: Emilio Ribas or Man-
daqui.

BCG vaccination

Routine BCG vaccination (Moreau–Rio de Janeiro
strain)[c] is compulsory in Brazil as part of a
programme established by the Ministry of Health. It
is recommended that the vaccine be given to children,
without a previous tuberculin test, between birth and
the end of their first year of life. Although BCG is
widely used the protection afforded by it has never
been assessed in Brazil.

Selection of cases

All notified cases of tuberculous meningitis which
were admitted to the Emilio Ribas or Mandaqui
Hospital from 1 January 1981 to 31 December 1983
that involved patients who were born after 1978
(coverage with intradermal BCG became high in
Brazil only from 1979) were ascertained. Because of
the difficulties in diagnosing tuberculous meningitis
unequivocally, criteria were defined based on clinical
and epidemiological findings, as well as on the results
of bacilloscopy, culture of cerebrospinal fluid (CSF),
and necropsy. All cases selected were residents of
MRSP.

Data on cases were collected in two question-
naires: one based on the hospital records and the
other on household interviews to clarify and com-
plement the hospital record data, particularly in
relation to the BCG vaccination status of the chil-
dren. The vaccination status of children was deter-
mined from their vaccination cards and, if possible,
by the presence of vaccination scars. Cases were
classified as BCG-positive only if their date of vaccin-
ation preceded that of diagnosis of tuberculous men-
ingitis. In situations where a case died, the child
concerned was still included in the study and a
household visit was made. The mother was then
questioned about the dead child's BCG vaccination
status and was asked to produce the vaccination
card. If the mother had lost the child's card, health
centre archives were searched. The mother's word
was accepted only if she affirmed that her child had
never been vaccinated, and such children were clas-
sified as unvaccinated. Cases were excluded from the
analysis if they could not be located or information
could not be obtained about their vaccination status.

Selection of controls

Neighbourhood controls. Cases and controls were
matched by home area and socioeconomic stratum.
In order to obtain a minimum of four suitable
controls per case, eight potential controls were

sought from children in the neighbourhood of each case. The mother of the index child was asked to nominate two children of neighbours, each of whose mothers nominated two more. This process was continued until eight controls were identified. The only requisite was that the children nominated should have been born after 1978. Information on controls was collected during home visits, using a very similar questionnaire to that used for cases. To determine the BCG vaccination status of the neighbourhood controls, the same procedure was used as for cases, and only those children whose vaccination status was known with certainty were accepted. Children who had a past or present history of tuberculosis were rejected as controls.

Hospital controls. In order to detect any biases that might have been introduced by the neighbourhood controls, a second series of controls was selected from patients in Emilio Ribas Hospital. In order to ensure that there was one suitable hospital control for each case, attempts were made to identify three potential controls per case.

Hospital controls who were suspected to have had tuberculosis were excluded. Also, children with diseases which could have been prevented by vaccination, e.g., measles or diphtheria, were also excluded, because it was considered likely that those not vaccinated against these diseases would have had less chance of having received BCG vaccine. The hospital controls were selected from patients admitted with meningitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* and who also satisfied the matching requirements of sex, home area, date of birth, and date of admission to hospital ± 6 months with respect to that of the index case.

Two questionnaires were used for hospital controls, one to obtain hospital records data and the other, which was similar to that for the neighbourhood controls, for the home visit. The BCG vaccination status of the hospital controls was determined in the same way as that of the cases and neighbourhood controls.

Sample size and estimation of vaccine efficacy

With the number of cases that were expected to be found during the study period and the level of BCG coverage, it was concluded that vaccine efficacy above 50% could be detected at the 5% level of significance at a power of 80%.

Vaccine efficacy was estimated from the relationship $1 - RR$ (*21*), where RR is the relative risk of tuberculous meningitis among the vaccinated compared to the unvaccinated children, estimated from the odds ratio. The odds ratio was calculated by conditional logistic regression analysis for matched case–control studies, using the EGRET software package (*10*).

Results

Characteristics of the study population

During the study period, a total of 474 cases of tuberculous meningitis were notified in São Paulo State, 196 (41.4%) of which involved 0–4-year-olds. In the two hospitals where the investigation was carried out, 271 diagnosed cases of tuberculous meningitis were admitted, 115 (42.4%) of which were children aged less than 5 years. Any case that transferred between the two hospitals or which was re-admitted was counted only once, using the initial admission to the first hospital in the respective year. A total of 94 eligible cases remained, 19 of which were omitted from the study (11 were born outside the study area, while eight could not be located). Of these 75 cases that were located and visited, there was uncertainty about the true vaccination status of two children, who were therefore also eliminated from the study. Also a control could not be obtained for one case, which was therefore removed. Altogether, 72 cases fulfilled the study criteria (25 cases from 1981, 24 from 1982, and 23 from 1983).

For these 72 cases, which formed the basis of the study, the history of contact with tuberculosis patients was traced for 46 of them (63.9%). Chest X-rays were available for only 50 of the 72 cases, and 46 (92%) were positive for tuberculosis. The results of CSF cultures were available for all cases, and *Mycobacterium tuberculosis* was isolated from 10 children (13.9%). The results of CSF smears for acid-fast bacilli were available for all cases and were positive for four children (5.5%). The overall case fatality rate was 50%, but was higher among those aged less than 1 year (60.5%). Of children who survived, many suffered neurological sequelae from which they recuperated with difficulty. Only 11 of the children investigated recovered without exhibiting apparent neurological abnormalities (Table 1).

A total of 520 neighbourhood controls and 83 hospital controls were visited. Of the neighbourhood controls, 15 were omitted (12 were born outside the defined study area, one was being treated for pulmonary tuberculosis during the period in which he was visited, and for two others doubts remained as to their true vaccination status). Neighbourhood controls could not be located for four cases. Of the 83 hospital controls, two were omitted (one was born outside MRSP and there were doubts about the vaccination status of the other), leaving 81. Hospital controls could not be obtained for 12 cases.

Table 1: **Clinical outcome of the 72 cases of tuberculous meningitis that formed the basis of the study, São Paulo, Brazil**

Outcome	No. of cases
Died in hospital	36 (50.0)[a]
Died after discharge from hospital[b]	2 (2.8)
Neurological sequelae	23 (31.9)
No apparent neurological sequelae	11 (15.3)
Total	72 (100.0)

[a] Figures in parentheses are percentages.
[b] Death was verified at a home visit.

Table 2 shows the distribution of cases and controls by age, sex and socioeconomic status (defined in terms of family income, area of residence, degree of domestic crowding, and mother's education level), and vaccination status. For ease of presentation, unmatched data are shown; however, matching

Table 2: **Characteristics of the study cases and controls, São Paulo, Brazil**

Characteristic	No. of cases	No. of neighbourhood controls	No. of hospital controls
Age			
<6 months	14 (19.4)[a]	35 (6.9)	20 (24.7)
6–11 months	30 (41.7)	36 (7.1)	34 (42.0)
12–23 months	21 (29.2)	104 (20.6)	18 (22.2)
≥24 months	7 (9.7)	330 (65.3)	9 (11.1)
Sex			
Male	49 (68.1)	250 (49.5)	51 (63.0)
Female	23 (31.9)	255 (50.5)	30 (37.0)
Socioeconomic status[b]			
1	58 (80.6)	431 (85.3)	55 (67.9)
2	13 (18.1)	74 (14.7)	26 (32.1)
Unknown	1 (1.4)		
Vaccination status			
Vaccinated	42 (58.3)	463 (91.7)	72 (88.9)
Unvaccinated	30 (41.7)	42 (8.3)	9 (11.1)
Total	72	505	81

[a] Figures in parentheses are percentages.
[b] Children were classified as socioeconomic status 1 if they satisfied at least three of the following conditions: per capita household income less than one minimum wage (about US$ 58.26 in May 1986); greater than four persons per bedroom; resident in the peripheral area of São Paulo municipality or other municipalities of the Metropolitan Region of São Paulo; and mother illiterate or only partly literate.

was preserved to estimate vaccine efficacy. Two-thirds of subjects came from the municipality of São Paulo, most from the peripheral poorer areas, while the remainder were from the other 36 municipalities of MRSP. Hospital controls were matched by sex and by age (within 6 months) but differed from cases with respect to their socioeconomic status, more frequently coming from higher status groups. Neighbourhood controls, as expected, had the same socioeconomic status as cases, but were older and had a higher proportion of females.

Efficacy of BCG vaccination

Vaccine efficacy was calculated separately for each group of controls using a conditional logistic regression analysis, and the results are shown in Table 3. The efficacies obtained were similar and high, the efficacy for neighbourhood controls (84.5%) being slightly greater than that for hospital controls (80.2%). No significant interactions were found between vaccination status and sex, age, or socioeconomic status.

Discussion

To the best of our knowledge, this is the first large study to quantify the effect of BCG vaccination against tuberculous meningitis. Previously, Miceli et al. in a case–control study in Argentina reported that BCG vaccination had an efficacy of 100% against this form of tuberculosis, although the sample size was small (*13*). Our results indicate that in the study community in São Paulo, BCG vaccination was highly effective against tuberculous meningitis in children below 5 years of age. This finding is very encouraging for the prevention of a disease that has a high fatality rate and serious neurological sequelae among many of those who survive. Tuberculous meningitis predominantly affects children from

Table 3: **Efficacy of BCG vaccination against tuberculous meningitis for matched pairs of cases and controls, São Paulo, Brazil**

	Vaccine efficacy (%)
Cases and neighbourhood controls[a]	84.5 (66.7–92.8%)[b]
Cases and hospital controls[c]	80.2 (40.6–93.4%)

[a] Adjusted for age, sex, and socioeconomic status.
[b] Figures in parentheses are the 95% confidence intervals.
[c] Adjusted for socioeconomic status.

poorer socioeconomic and environmental backgrounds, who may also be less likely to have been vaccinated with BCG. Since the majority of cases occur among children aged 3–11 months, we recommend that BCG vaccine be administered within the first 3 months of life and that efforts are made to achieve a high coverage across all socioeconomic strata.

Use of the case–control approach has been recommended for studies of the effectiveness of BCG vaccination (15, 21, 22). Compared with controlled trials, the case–control approach is both quicker to carry out and cheaper. In accord with the reports of other workers (13, 19, 23), our findings indicate that the case–control method is useful for evaluating the effectiveness of BCG vaccination. It is particularly encouraging that similar results were obtained with the two groups of controls. Hospital controls, although easy to locate, differed from cases with respect to socioeconomic status. The neighbourhood controls, although they had the same socioeconomic status as the cases, differed from the latter in their age and sex distributions; they were, however, a more plentiful source of controls. The analysis with each group of controls therefore still required some control of confounding variables, which led to similar estimates of BCG efficacy. The vaccine efficacy was slightly higher for neighbourhood controls, but this may have arisen because of further confounding. No evidence was found for interactions between vaccination status and age, sex, or socioeconomic status, but the sample size was rather small to study these effects.

In most countries where tuberculosis is endemic, its incidence has remained fairly constant. For such countries, BCG vaccination is an attractive policy to protect children against tuberculosis, although it does not significantly decrease transmission of the disease. Our results are encouraging for the prevention of tuberculous meningitis and should hopefully stimulate further case–control studies of BCG vaccination and childhood tuberculosis in other countries.

Résumé

Efficacité de la vaccination par le BCG contre la méningite tuberculeuse: étude cas-témoins à São Paulo, Brésil

A l'approche de la fin du XXe siècle, la tuberculose pose encore un problème de santé publique, notamment dans les pays en développement. Pour y remédier, les organismes sanitaires internationaux ont décidé d'axer les programmes de lutte sur l'identification et le traitement des cas de maladie et sur la vaccination par le BCG.

Bien que le vaccin BCG soit largement utilisé dans le monde à titre de mesure préventive contre la tuberculose, sa valeur a été remise en question. L'article présente une discussion du rôle du BCG en tant que mesure de lutte contre la tuberculose et étudie la protection qu'il confère contre la méningite tuberculeuse.

Les politiques de vaccination par le BCG dans les Etats brésiliens de Rio Grande do Sul et de São Paulo, qui ont différents calendriers vaccinaux, ont été évaluées; on a pour cela examiné l'incidence de la méningite tuberculeuse dans chacun de ces Etats. Dans l'Etat de Rio Grande do Sul, où les enfants sont vaccinés à l'âge de sept ans, l'incidence de la méningite tuberculeuse est environ quatre fois plus élevée qu'à São Paulo où les enfants sont vaccinés avant l'âge d'un an. La couverture vaccinale du BCG varie sensiblement d'une région à l'autre du Brésil. Par exemple, en ville de São Paulo, elle est très élevée, dépassant même 100% selon les chiffres officiels; toutefois, une enquête réalisée en 1982–1983 conduit à estimer à 88% la couverture vaccinale chez les enfants de moins de 18 mois. L'article rapporte les résultats d'une étude cas-témoins menée dans la zone urbaine de São Paulo (Brésil) afin de déterminer la protection que confère le BCG contre la méningite tuberculeuse chez les enfants de moins de cinq ans.

L'étude a porté sur 72 cas de méningite tuberculeuse, 505 témoins de voisinage et 81 témoins hospitaliers. On a calculé l'efficacité du vaccin selon la formule 1-RR, dans laquelle RR est le risque relatif de méningite tuberculeuse chez les sujets vaccinés par rapport aux sujets non vaccinés, exprimé par le odds ratio. Avec une analyse de régression logistique conditionnelle, nous avons calculé que l'efficacité du vaccin était analogue dans les deux groupes de témoins, légèrement plus grande toutefois chez les témoins de voisinage (84,5%) que chez les témoins hospitaliers (80,2%). On n'a observé aucune relation

significative entre l'état vaccinal et le sexe, l'âge ou le niveau socio-économique.

Bien que des réserves aient été exprimées quant à l'efficacité du BCG sur la chaîne de transmission de la tuberculose et par conséquent sur l'incidence et la mortalité générale dues à cette maladie, nos observations montrent qu'il peut être utile s'il protège contre les formes infantiles graves de tuberculose. Comme la plupart des cas de méningite tuberculeuse chez l'enfant surviennent chez les nourrissons de 3 à 11 mois, nous recommandons d'administrer le BCG au cours des trois premiers mois de la vie.

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