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The effectiveness of BCG vaccination of the newborn against childhood tuberculosis in Bangkok*

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Child contacts of newly detected cases of smear-positive pulmonary tuberculosis were registered and followed up during fortnightly home visits; clinical and radiological examinations were carried out at the time of registration and three months later. As many as 218 out of 1506 children showed clinical or radiological evidence suggestive of tuberculosis. In the children who had received BCG vaccination after birth this evidence was found half as often as in the unvaccinated children. This shows that the BCG vaccination programme in Bangkok has an appreciable effect in preventing childhood tuberculosis and, most probably, also the late consequences of intrafamilial infection in early life.

INTRODUCTION

Role of BCG vaccination

Tuberculosis control programmes in developing countries nearly always make use of sputum microscopy in the investigation of persons presenting with symptoms of pulmonary tuberculosis. They also offer ambulatory treatment to the patients so diagnosed, and provide BCG vaccination for newborn or young infants. With this method of case-finding, however, young tuberculosis patients often remain undetected because the sputum is swallowed or, if some sputum is obtained, it contains too few bacilli. Children may develop rapidly evolutive forms of tuberculosis such as meningitis and miliary disease, which are highly fatal, but usually they have a mild respiratory disease or remain symptomless with a primary complex which may cause overt disease later on. This type of "passive" case-finding and treatment programme in the developing countries can lead to only a marginal decrease in the risk of infection, the benefit to the lower age group being minimal. The situation is aggravated by the fact that young children mainly contract tuberculosis through intrafamilial transmission and are often infected before the source of transmission is detected.

BCG vaccination soon after birth may not only protect against the acute manifestations of childhood tuberculosis but also, in the long run, contribute significantly to the elimination of tuberculosis. The childhood forms of tuberculosis are hardly infectious and it has been argued that their prevention would not decrease the risk of infection in the community. It is also unlikely that a single BCG vaccination at birth will provide protection against pulmonary tuberculosis infection during adolescence or later in life. But vaccination may reduce the lifelong risk of endogenous reactivation associated with foci acquired from infection during childhood. The pathogenesis of tuberculosis in developing countries is not well known, but in Europe the importance of intrafamilial infection of children used to be such that, before Koch's discovery, tuberculosis was thought to be a hereditary disease.

Effectiveness

In view of its potential for tuberculosis control, BCG vaccination has been widely used in developing countries and notably is included in the Expanded Programme on Immunization. The problem is that the effectiveness of BCG vaccination at birth in developing countries is not known. Evidence obtained in European countries and North America is on the whole very favourable (*1*). Controlled clinical trials in adolescents and young adults carried out in

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the past showed contradictory results (*2*), and the latest large-scale community trial, carried out in south India, showed that BCG vaccination conferred no protection whatsoever against bacteriologically confirmed pulmonary tuberculosis (*3*). These findings seriously challenged the practice of BCG vaccination in developing countries. A WHO Study Group (*4*) nevertheless recommended that vaccination of infants should be continued. One consideration was that the result observed in south India did not necessarily apply to vaccination of the newborn. Childhood tuberculosis had not been observed in the trial, and the leading hypothesis to explain lack of protection—i.e., that infection with mycobacteria other than *Mycobacterium tuberculosis* provided a level of protection to which BCG could not add significantly—obviously would not apply if vaccination is given soon after birth. Indeed, more recent observations (*5*) appear to confirm that the children in the Indian trial (0–14 years of age at the time of intake) do show some protection against tuberculosis of the adult type.

A further recommendation of the Study Group, confirming that of an ICMR/WHO Scientific Group (*6*), was that research on the effectiveness of BCG vaccination in young children should be undertaken according to methods applicable in developing countries. WHO assumed responsibility for the coordination and monitoring of the research programme and provided outlines for case-control and contact studies. The Central Chest Clinic, Bangkok, cooperated in the programme by undertaking a study among child contacts of newly discovered sputum-smear-positive patients with pulmonary tuberculosis.

MATERIALS AND METHODS

Intake

The study design resembles that of a controlled trial except that it was retrospective as regards vaccination. This means that the vaccinated and the control groups were not randomly selected, and for this reason a number of measures were taken to allow for the comparability of the groups to be verified and for adjustments to be made if necessary. Taking advantage of the fact that tuberculosis in young children in most cases stems from intrafamilial infection, the intake was restricted to household child contacts, up to the age of 5 years, of smear-positive patients newly detected at the Central Chest Clinic in Bangkok. Apart from the tremendous savings in the cost of active follow-up, this procedure itself ensured a certain comparability as regards exposure to infection.

To obtain further information on the degree of exposure, a note was made of the relationship between the sources of infection and the child participants and of whether the child slept in the same room as the source of the infection. As an indicator of socioeconomic status of the household a record was made of the number of persons per room; and as an indicator of knowledge, attitude and practice, a note was made of whether the child had been born in hospital or at home and whether the child had been breast-fed, formula-fed, or both during the first six months after birth. For each child the nutritional status was determined according to the weight-for-height classification for Thai children.

Age, sex, and addresses were recorded, and the latter were plotted on a large map of the town by means of small flags of different colours for vaccinated and unvaccinated children so that the distribution in each of 20 sectors could be easily verified. Finally, since the household addresses were obtained from the index cases, refusal of the clinical and X-ray examinations was considered a useful indicator of possible selection for vaccination.

Vaccination status

A drawback of the retrospective intake was that no accurate vaccination records were available centrally. Since BCG vaccination leaves a characteristic scar in the large majority of vaccinated children, the presence of such a scar was taken as an indicator of vaccination. At the first home visit the children were examined for the presence of a scar and its size was recorded. However, some children without a scar might have had BCG vaccination and a check was therefore made of whether the children had a vaccination certificate or had been registered as vaccinated at the hospital where they were born. At the outset, it was assumed that birth in hospital would be associated with a higher probability of vaccination than birth at home, but since it appeared that almost all children were born in hospital, this information had no practical value in discriminating between the two groups.

In Bangkok, BCG vaccination is routinely carried out in all maternity wards, the vaccine for this programme being obtained from the Institut Mérieux. During the period that the children were eligible for vaccination, 34 batches of 10-dose ampoules were received containing 1.7 ± 0.5 million culturable particles per dose according to the quality control tests performed before shipment.

Initial examination and follow-up

Within a week of the detection of the index case, a visit was made to the household and the personal data

mentioned above were taken. The contact children were then offered a clinical and X-ray examination. In practice, the survey teams invited the child, with another person, to accompany them; after visits to a few more homes they went to the Central Chest Clinic for the examinations, after which the children were taken back home. This procedure, rather than the issue of appointments, was shown to yield a very high participation rate.

On arrival in the Central Chest Clinic a clinical record was made out for each child contact. The site of BCG vaccination was then covered with a dressing (even if there had been no vaccination or scar) and the child was presented to the paediatrician for a clinical examination and a full-plate postero-anterior X-ray was made. The X-ray picture was examined by two readers. If one of them reported an abnormality or if there were clinical signs or symptoms of tuberculosis, the child was classified as a suspect and weekly home visits were made to follow the clinical course. If the child appeared to be healthy, the home visits were made fortnightly. During these visits the weight of the child and the temperature were measured and an assessment was made of the state of health based on visual impression and interviews with the mother. Whenever indicated, the children were re-examined.

The suspect children were followed up for as long as there were medical indications. Clinical and X-ray examinations were repeated on all the children after three months. If no abnormalities were found, the active follow-up of healthy children was discontinued but the parents were advised to report to the clinic if the child fell ill. At three months all the children were given a tuberculin test with 2 TU of RT23 with Tween. The results of these tests were not used for diagnostic purposes (as this might have caused bias between the vaccinated and unvaccinated children), but as an indicator of the risk of infection and of the sensitivity induced by the vaccinations.

When indicated by the clinical or X-ray examinations, a laryngeal swab was taken for culture and gland biopsies were made and examined by histopathology and culture. If tuberculosis was strongly suspected, treatment was started at once with rifampicin and isoniazid. In cases with doubtful pulmonary shadows a 15-day course of penicillin was given, after which another examination was made. The response to drug treatment was carefully recorded.

For each child a final diagnosis was made at the end of the study. At this time all the X-rays were read again by two readers, who were found to have a high level of agreement; intra-reader disagreement correlated highly with inter-reader disagreement. Cases showing disagreement were reviewed together by the two readers, with an umpire to decide in a few instances.

A scoring system proposed by WHO[a] was used to obtain an indication of the probability of tuberculosis. Scores were attributed to the various signs and symptoms reported, the X-ray findings, clinical findings, including the response to treatment, and the results of laboratory tests. The separate scores were added to make up a final score, except that non-specific signs and symptoms were disregarded if no other evidence of tuberculosis had been found.

RESULTS

Study population

The study was started in September 1981 and terminated in June 1984, after 971 index cases who reported contact with young children had been registered. Registration and initial examinations were completed for 1506 child contacts. The field teams could not trace 124 reported child contacts; in most of these cases it appeared that the family and sometimes the children had changed residence in the short period between detection of the index case and the first home visit. In the case of 8 children the initial examination was refused, in 4 of them (all with a BCG scar) after the contact card had been filled in.

The distribution of the study population is shown in Table 1. It is seen that participation decreased with increasing age; the older children especially were often difficult to trace. The proportion of boys among the participants was slightly higher than that of girls.

Vaccination status

As many as 1218 (81%) of the children had a BCG scar, and among those without a scar, 35 had a record of vaccination. Since two indicators of vaccination status were recorded (i.e., the presence or absence of a BCG scar and of a vaccination record), an estimate could be made of the number of vaccinated children among those who had neither a scar nor a record. On the assumption that the children with a scar or with a record had actually been vaccinated, and that the establishment and conservation of a record was independent of the development of a scar after vaccination, a total of 55 children ($745/473 \times 35$) among the 253 without a scar or a record must have been vaccinated. The incidence observed in the other

[a] Typical examples from the scoring system are a history of chronic cough or meningeal signs (+1), matted peripheral lymph nodes on clinical examination (+3), hilar adenitis on X-ray (+3), infiltration with cavity (+4), positive culture of laryngeal swab or lymph node aspirate (+7), rapid response to broad-spectrum antibiotics (−6), and radiological improvement without antituberculosis treatment (−3) or with antituberculosis treatment (+3).

Table 1. Study population by age, sex and vaccination status

Age (years)	Sex	No. of children with a BCG scar from a vaccination that was: Recorded	Not recorded	No. of children without a BCG scar from a vaccination that was: Recorded	Not recorded	Total "vaccinated"[a]
0–1	M	93	94	3	30 (21.1)[b]	190 (28.8)
	F	82	73	3	24 (21.6)	158 (26.6)
1–2	M	62	79	4	33 (23.2)	145 (22.0)
	F	60	84	4	20 (18.0)	148 (24.9)
2–3	M	47	89	7	24 (16.9)	143 (21.7)
	F	44	86	4	30 (27.0)	134 (22.6)
3–4	M	27	84	2	35 (24.6)	113 (17.1)
	F	30	69	5	25 (22.5)	104 (17.5)
4–5	M	15	52	1	20 (14.1)	68 (10.3)
	F	13	35	2	12 (10.8)	50 (8.4)
Total	Males	244	398	17	142 (99.9)	659 (99.9)
	Females	229	347	18	111 (99.9)	594 (100.0)
	Both	473	745	35	253	1253

[a] Comprising children with a BCG scar (recorded and not recorded) and those without a BCG scar (but recorded).
[b] Figures in parentheses are percentages.

vaccinated children could therefore be applied to these 55 children, and the incidences in the vaccinated and unvaccinated groups could be adjusted accordingly. Among the vaccinated children, 90 (7%) had no discernible scar; this percentage is not unusual for a routine vaccination programme.

Comparability

The high vaccination coverage increases the risk of selection for vaccination. This is an inherent weakness of studies in which the intake is not random because a spurious effect might occur, when calculating the effectiveness of vaccination, if *both* vaccination coverage *and* risk of disease are associated with certain group characteristics.

As may be seen from Tables 1 and 8, vaccination coverage as well as disease risk appeared to be associated with age. Stratification by age, however, showed that this did not affect the calculated effectiveness of BCG vaccination. Further data relevant to comparability of the vaccinated and unvaccinated child contacts are presented in some detail in Tables 2 to 6. To simplify the presentations, children with either a BCG scar or a vaccination record have been presented as "vaccinated", and those without either as "unvaccinated". Data are presented separately for the children who never showed a sign of disease that could point to tuberculosis (healthy children) and for those who did present such signs at the clinical or X-ray examination (suspects); this was done to make it possible to appreciate the significance of possible discrepancies. The distributions of the children finally classified as cases were very similar to those of the suspects and are therefore not presented.

Table 2 shows the relationship of the index cases to the child contacts who were healthy or suspect. Although there is some variation in the data, there is no striking relation between vaccination coverage or risk of disease and the different index cases.

An indication of the proximity of exposure to the index case may be obtained from Table 3. Differences in proximity are reflected in the incidence of disease, but vaccination status was not related to them.

Table 4 shows the influence of crowding (estimated by the number of persons per room) in the household. Clearly the living conditions of the majority could be described as very crowded. There is a small but statistically significant difference in vaccination coverage, but the risk of disease was not related to the number of people per room.

Table 2. Vaccination coverage according to the relationship of index cases to child contacts

Index case	No. of healthy children[a]		No. of suspects[b]	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Mother	139 (13.4)[c]	24 (12.8)	29 (13.3)	12 (18.2)
Father	249 (24.1)	62 (33.2)	70 (32.1)	14 (21.2)
Grandparent	335 (32.4)	59 (31.6)	56 (25.7)	20 (30.3)
Brother/sister	19 (1.8)	16 (8.6)	5 (2.3)	3 (4.5)
Other[d]	293 (28.3)	26 (13.9)	58 (26.6)	17 (25.8)
Total	1035	187	218	66

[a] Children who never showed a sign of disease pointing to tuberculosis.
[b] Children who, at the clinical or X-ray examinations, presented signs that pointed to tuberculosis.
[c] Figures in parentheses are percentages.
[d] Invariably an uncle or aunt.

Table 3. Vaccination coverage according to proximity to the index case

Proximity to index case	No. of healthy children[a]		No. of suspects[b]	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Occupying same bedroom	617 (59.6)[c]	118 (63.1)	148 (67.9)	43 (65.2)
Occupying different bedroom	418 (40.4)	69 (36.9)	70 (32.1)	23 (34.8)
Total	1035	187	218	66

[a] Children who never showed a sign of disease pointing to tuberculosis.
[b] Children who, at the clinical or X-ray examinations, presented signs that pointed to tuberculosis.
[c] Figures in parentheses are percentages.

Table 4. Vaccination coverage according to living conditions indicative of crowding

No. of persons per room	No. of healthy children[a]		No. of suspects[b]	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
<1	0	0	0	0
1-2	19 (1.8)[c]	1 (0.5)	8 (3.7)	0
2-3	191 (18.5)	15 (8.0)	44 (20.2)	5 (7.6)
3-4	322 (31.1)	67 (35.8)	69 (31.7)	24 (36.4)
⩾4	503 (48.6)	104 (55.6)	97 (44.5)	37 (56.1)
Total	1035	187	218	66

[a] Children who never showed a sign of disease pointing to tuberculosis.
[b] Children who, at the clinical or X-ray examinations, presented signs that pointed to tuberculosis.
[c] Figures in parentheses are percentages.

Table 5. Vaccination coverage according to feeding practices

	No. of healthy children[a]		No. of suspects[b]	
Feeding practice	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Breast fed	624 (60.3)[c]	119 (63.6)	117 (53.7)	39 (59.1)
Formula fed	329 (31.8)	53 (28.3)	67 (30.7)	14 (21.2)
Both	82 (7.9)	15 (8.0)	34 (15.6)	13 (19.7)
Total	1035	187	218	66

[a] Children who never showed a sign of disease pointing to tuberculosis.
[b] Children who, at the clinical or X-ray examinations, presented signs that pointed to tuberculosis.
[c] Figures in parentheses are percentages.

Table 6. Vaccination coverage according to nutritional status

	No. of healthy children[a]		No. of suspects[b]	
Nutritional status	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Normal	557 (53.8)[c]	89 (47.6)	124 (56.9)	30 (45.5)
Malnutrition				
First degree	328 (31.7)	57 (30.5)	69 (31.7)	27 (40.9)
Second degree	53 (5.1)	17 (9.1)	17 (7.8)	3 (4.5)
Third degree	13 (1.3)	1 (0.5)	2 (0.9)	0
No information	84 (8.1)	23 (12.3)	6 (2.8)	6 (9.1)
Total	1035	187	218	66

[a] Children who never showed a sign of disease pointing to tuberculosis.
[b] Children who, at the clinical or X-ray examinations, presented signs that pointed to tuberculosis.
[c] Figures in parentheses are percentages.

From Table 5 it may be seen that the feeding practices were very similar among both vaccinated and unvaccinated healthy children. Formula feeding as well as breast-feeding seem to be associated with a slight decrease in the risk of disease and mixed feeding with an increase. But there was no association between feeding practice and vaccination status.

Table 6 shows that the vaccinated healthy children were slightly better fed than the unvaccinated ones, but the same was seen among the suspects. The nutritional status apparently did not influence the risk of disease. The association of nutritional status with vaccination status was therefore irrelevant as regards the effectiveness of vaccination.

In summary, apart from age, no differences between the vaccinated and unvaccinated children were observed that call for stratification of the material. The vaccinated and unvaccinated children appeared comparable as regards all the variables studied. Since there were only 8 refusals, the proportion of refusals scarcely gives information on possible selection for vaccination, but the fact that 4 of these children (for whom the vaccination status was known) had a BCG scar does not substantiate this possibility. It may be noted that the cooperation among vaccinated and unvaccinated groups was not significantly different, as is shown by the acceptance of the tuberculin test (see Table 10).

Diagnosis

Prospective case-finding for tuberculosis in young children is extremely difficult. Bacteriological

diagnosis would produce a large underestimate of the incidence, and clinical/radiological diagnosis an overestimate, especially if the actual incidence is low. But by limiting the case-finding activities to contacts and furthermore to the most vulnerable period, the incidence of tuberculosis in the study population is greatly increased and less specific diagnostic tests may produce a fairly accurate result. Nevertheless, the probability of having reached the correct diagnosis may vary from case to case. To be able to take account of this, the scoring system was applied to the various findings, and to ensure uniformity of interpretation the final score (on the probable diagnosis) was determined when the study had been terminated.

The distribution of the final scores in suspects is shown in Table 7. The healthy children, by definition, all had a score of 0. Some final scores that turned out negative have been included under 0–1. In view of the observed bimodal distribution, children with scores of 0–1 probably include relatively few cases of tuberculosis and therefore have not been considered as such. Only children with final scores of 2 or more were considered as cases. Hilar adenitis was the most frequently observed type of disease.

Table 7. Distribution of final scores in suspects by type of disease

Score	Hilar adenitis	Infiltration	Both[a]	Total
0–1	51	6	9	66
2–3	6	1	1	8
4–5	6	2	1	9
6–7	14	7	6	27
8–9	37	18	6	61
10–11	25	12	19	56
12–13	11	3	18	32
14–15	–	1	9	10
16–17	2	3	4	9
18–19	2	–	2	4
⩾20	–	1	1	2
Total	154	54	76	284

[a] Includes 4 cases of cervical lymphadenitis and 2 cases of tuberculosis of the spine.

Table 8. Incidence of tuberculosis (scores 2+) by age, sex and vaccination status

		No. of children with a BCG scar from a vaccination that was:		No. of children without a BCG scar from a vaccination that was:		
Age (years)	Sex	Recorded	Not recorded	Recorded	Not recorded	Total
0–1	M	7	9		5	21 (18.8)[a]
	F	5	8		2	15 (14.2)
1–2	M	7	12		13	32 (28.6)
	F	14	17	1	5	37 (34.9)
2–3	M	5	17		6	28 (25.0)
	F	7	15		4	26 (24.5)
3–4	M	5	8	1	6	20 (17.9)
	F	3	7		9	19 (16.0)
4–5	M	2	1		8	11 (9.8)
	F	2	5		2	9 (8.5)
Total	Males	26	47	1	38	112
	Females	31	52	1	22	106
	Both	57	99	2	60	218

[a] Figures in parentheses are percentages.

Table 9. Incidence of tuberculosis (scores 2+) by type of disease and vaccination status

Type of tuberculosis	No. of children with a BCG scar from a vaccination that was:		No. of children without a BCG scar from a vaccination that was:		Total
	Recorded	Not recorded	Recorded	Not recorded	
Hilar adenitis	28	51		24	103
Infiltration	12	21	2	13	48
Both and other types	18	26		23	67
Total	58	98	2	60	218

Incidence of tuberculosis

As noted in the preceding tables, 284 tuberculosis suspects were found, 218 among the 1253 vaccinated and 66 among the 253 unvaccinated participants. The incidence of tuberculosis (defined as score 2+) is shown by age, sex and vaccination status in Table 8 and by type of disease in Table 9. Relating these data to the study population (Table 1), the total incidence was 14.5%; 14% in boys and 15% in girls. Among the vaccinated the incidence was 12.6% and among the unvaccinated it was 23.6%. This difference is significant statistically ($P<0.001$). Among the vaccinated the incidence was 11.2% in boys and 14.2% in girls, whereas among the unvaccinated it was 26.8% in boys and 19.6% in girls. The difference in boys is significant statistically ($P<0.001$), but not that in girls.

Regarding the type of disease, the incidences in the vaccinated and unvaccinated, respectively, were 6.3% and 9.4% for hilar adenitis, 2.8% and 5.1% for infiltration, and 3.5% and 9.0% for both and others. Only the last difference is significant statistically ($P<0.001$).

As mentioned before, in these calculations "vaccinated" refers to children with a scar or a vaccination record and "unvaccinated" to children without either of these. The absence of a scar in a vaccinated child may have been due to the use of insufficient vaccine; for practical purposes therefore children with a scar may be considered as vaccinated and all those without a scar as unvaccinated. Any error in this assumption would only marginally influence the incidences in the present study.

Efficacy and effectiveness

It is conventional to indicate the efficacy, or protective effect, of vaccination as the ratio of the percentage difference between the incidences in unvaccinated and vaccinated children to the incidence in the unvaccinated. The resulting figure can be applied whatever the incidence to estimate the potential effectiveness of vaccination in a given population, i.e., the number of cases prevented. However, extrapolation to another situation may not be justified. A further problem is that the efficacy will depend on the diagnostic technique used. If the diagnostic test is not very specific, persons without tuberculosis may be included among the "cases" and the efficacy will be underestimated. A highly specific test, such as culture, will have a relatively low sensitivity and may lead to an underestimation of the incidence and thus of the effectiveness. These problems are very much amplified in studies on tuberculosis in young children.

In the present study there were 11 cases confirmed by bacteriology or histology, 6 of them with a scar and 5 without, corresponding to an efficacy of some 72%. But considering the low incidence of confirmed cases (the wide confidence interval apart), it would appear that, in terms of effectiveness, not more than some 18 cases were prevented. For children with both hilar adenitis and infiltration or other types of tuberculosis (including most of the confirmed cases) the efficacy appeared to be 61%, which means that some 69 such cases were prevented. This example shows that a less stringent criterion may show a lower efficacy but a higher effectiveness.

Based on the data in Tables 1 and 8, and adjusting for the estimated 55 vaccinated children included among those without a scar or a vaccination record, the observed efficacy is 53% with 95% confidence limits of 64% and 38%; the observed number of cases among the vaccinated is 185 less than expected. Thus, although the efficacy appears less, the effectiveness is far higher than with a more stringent diagnostic

Table 10. Tuberculin reactions (to 2 TU of RT 23 with Tween 80) by score and vaccination status

Reaction size (mm)	No. of healthy children		No. of cases (score 2+)	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
0–4	471 (50.9)[a]	100 (62.9)	40 (26.4)	16 (26.2)
5–9	8 (0.9)	2 (1.3)	–	–
10–14	170 (18.4)	9 (5.7)	20 (13.2)	8 (13.1)
15–19	135 (14.6)	21 (13.2)	39 (25.8)	15 (24.5)
20–24	122 (13.2)	26 (16.4)	48 (31.7)	21 (34.4)
25–29	16 (1.7)	1 (0.6)	2 (1.3)	–
⩾30	3 (0.3)	–	2 (1.3)	1 (1.6)
Total	925	159	151	61
(Not given or not read)	110 (10.6)	28 (15.0)	5 (3.2)	1 (1.6)

[a] Figures in parentheses are percentages.

criterion. On the other hand, consideration of all the suspects produces both a lower efficacy and a lower effectiveness, which confirms that a certain diagnostic rigour is advantageous. Adopting a higher score than 2+ as the criterion for a "case" produces only a slightly higher efficacy but a lower effectiveness.

Efficacy varied with age, but turned out to be similar in the 0–2 and 4–5-year age groups. Thus the effectiveness of BCG vaccination does not seem to wane in the first years of life.

The results of the tuberculin tests, performed some three months after the detection of the index cases, are shown in Table 10. The percentage of healthy contacts with reactions of 0–4 mm is 12% lower among the vaccinated than among the unvaccinated, but still is about 50%. There was no apparent effect at all as regards the reactions of 15 mm or larger. BCG vaccination had only a modest effect on tuberculin sensitivity. Among the cases (score 2+), the tuberculin reactions for both vaccinated and unvaccinated groups were similar and, compared with the reactions in the healthy children, there were higher proportions with large reactions. Thus, immunologically, these cases as a group clearly differed from the healthy children.

DISCUSSION

The method described in this study appears to offer a practical alternative to the classical controlled trial technique for evaluating the effectiveness of BCG vaccination. The application of systematic intake and prospective follow-up, at least to some extent, makes it possible to compare the vaccinated and the unvaccinated groups and helps exclude various sources of bias that may influence fully retrospective studies. A distinct advantage is that the results are relevant to the real-life situation of a routine vaccination programme compared with the artificial conditions of a controlled trial.

A relatively large number of cases could be detected by following up a small population. Since in a vaccination study it is the number of cases found, rather than the size of the study population, that determines the power of the experiment, an excellent test situation is created. In this respect the present study, with 218 cases, ranks below the BCG trials carried out among American Indians (*7*) and British adolescents (*8*), in which, after prolonged follow-up, about 300 cases had been accumulated, but it compares well with the latest trial in India, for which the first analysis was based on 72 cases (*3*) and that after 12.5 years on 285 cases of all ages (*5*), and certainly with the trials in Illinois (*9*) and in Georgian schoolchildren (*10*) where there were no more than 20 and 8 cases respectively.[b] In the present study, however, the experimental power was somewhat reduced because of the high vaccination coverage.

An incidence of some 25% in the unvaccinated group may seem very high, especially since the observation period was only about three months, but

[b] These are the studies in which BCG vaccination was shown to have no protective effect.

it should be noted that most cases were detected at the first examination. The figure in actual fact represents a prevalence, or risk associated with being a contact, rather than a three-monthly incidence. As such, it is similar to that found in contact studies in India (*11*). When Calmette introduced BCG vaccination the estimated risk of *death* from tuberculosis among child contacts in several European countries was as high as 25% (*12*), evidently because of the continuous exposure. Prompt chemotherapy of infectious cases, which should diminish the risk of disease for child contacts, is often not achieved in developing countries. Since intensive exposure carries an increased risk of disease, it may be that it is not the first infection but a reinfection that leads to tuberculosis. In such cases the fact of having been vaccinated at birth cannot be expected to lower the risk of disease: the level of immunity is probably determined by the first infection, whether BCG vaccination was given or not (*13*).

The mechanism of immunity in tuberculosis appears to rest on the prevention of haematogenous spread, not on the prevention of infection or of spread from the site of infection to the nearest draining lymph nodes. The observation of enlarged hilar lymph nodes on X-ray examination may therefore not be of great relevance to the efficacy of BCG vaccination. This was verified in a limited series in which the routine addition of a lateral X-ray picture revealed hilar lymph node enlargement in almost 40% of the children. Inclusion of cases of uncomplicated lymph node enlargement as cases of tuberculosis, especially when this is as frequent as in the present study, may substantially decrease the *observed* efficacy of BCG vaccination. What really matters is whether the lymph node enlargement leads to local complications or to tuberculous foci anywhere in the body through haematogenous dissemination. Investigating this would have required prolonged follow-up, which for practical and obvious ethical reasons was not possible. Chemotherapy with isoniazid and rifampicin was provided as soon as tuberculosis was suspected in a participant. Probably thanks to this, not a single case of tuberculous meningitis or miliary tuberculosis occurred. Still, it seems reasonable to assume that the incidences of these types would decrease like those of other forms of tuberculosis that depend on haematogenous dissemination, and that the efficacy of BCG vaccination may well be higher than can be observed in a three-monthly period as seen in children with hilar lesions plus infiltration and other forms.

In terms of induced tuberculin sensitivity, the effect of the vaccination was low. This may have been due to the vaccine used, the dose, or the handling of the vaccine in the programme. Although the relationship in man between protection and tuberculin sensitivity is not known, it may well be that the vaccinations were unnecessarily "weak" and the resulting protection was suboptimal.

The larger tuberculin reactions apparently were the result of infection rather than of BCG vaccination. Their correlation with the diagnostic findings was extremely poor, as demonstrated by the fact that as many as 30% of the cases (including bacteriologically confirmed ones) did not react to tuberculin. This confirms that the tuberculin test is of doubtful diagnostic value in child contacts. It nevertheless is clear that a large proportion of the child contacts are infected before the index case is detected. This is in agreement with the observations made in Madras (*11*) and confirms that the current tuberculosis programmes have a limited, if any, effect on intrafamilial transmission of infection. It also confirms the recommendation of the WHO Study Group (*4*) that BCG vaccination should be given as early in life as possible.

The efficacy in boys (61%) appears higher than in girls (32%) but this difference is not statistically significant and is probably attributable to chance. Further studies within WHO's programme on the evaluation of BCG vaccination may clarify this matter.

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RÉSUMÉ

EFFICACITÉ DE LA VACCINATION DES NOUVEAU-NÉS PAR LE BCG DANS LA LUTTE CONTRE LA TUBERCULOSE INFANTILE À BANGKOK

La vaccination des nouveau-nés et des jeunes nourrissons par le BCG est largement utilisée dans les pays en développement comme mesure de lutte contre les formes graves de tuberculose infantile. Son efficacité est toutefois mal connue. L'exécution d'essais contrôlés chez les jeunes enfants est extrêmement longue et coûteuse, et comporte de graves difficultés techniques. De plus, comme les données dont on dispose sur l'efficacité de la vaccination chez les enfants sont assez favorables, l'utilisation d'un vaste groupe témoin non vacciné soulève des problèmes éthiques. L'OMS a par conséquent proposé un programme d'études relativement simples destinées à examiner la question de la vaccination par le BCG après qu'un essai réalisé sur une communauté en Inde ait donné des résultats très décevants. Dans le cadre de ce programme, on a évalué l'efficacité de la vaccination des nouveau-nés par le BCG à Bangkok en déterminant l'incidence de la tuberculose chez les contacts âgés de moins de cinq ans de malades chez lesquels a été récemment diagnostiquée une tuberculose pulmonaire à frottis positif.

Sur le plan technique, l'inconvénient de cette méthode réside dans le fait que les groupes vaccinés et non vaccinés n'ont pas été constitués au hasard; on a donc procédé à plusieurs observations pour vérifier la comparabilité de ces groupes. Les paramètres examinés, outre l'âge et le sexe, portaient sur les pratiques familiales en matière d'alimentation, l'état nutritionnel, la situation socio-économique, l'intensité de l'exposition et la source de l'infection. On a également tenu compte de l'assiduité aux examens de suivi.

La méthode a en revanche pour avantages qu'on peut trouver un grand nombre de cas dans une petite population, qu'il n'y a pas de perte de temps au niveau de la répartition en groupes et de la décision de vacciner, et que le suivi est très bref. Grâce à ces facteurs, l'étude est relativement peu coûteuse. Un autre avantage peut-être moins net réside dans le fait que, grâce à la proportion relativement élevée de cas, les épreuves diagnostiques sont beaucoup plus efficaces. Enfin, les résultats s'appliquent directement aux conditions réelles d'un programme, et il n'est pas nécessaire d'extrapoler à partir des conditions "artificielles" des essais contrôlés.

Pour déterminer l'état vaccinal des enfants, on a recherché la présence d'une cicatrice de vaccination et on a vérifié les registres de vaccination par le BCG. On n'a pas trouvé de différences justifiant une stratification des données.

Au cours des trois années de l'étude, 284 sujets suspects ont été trouvés sur 1507 participants. Les données cliniques et radiologiques ont été examinées à la fin de l'étude et un système de cotation a été appliqué aux résultats. Selon ce système, 218 enfants ont été classés comme "cas". Parmi ces cas, 158 ont été observés chez les 1253 enfants vaccinés et 60 chez les 253 enfants non vaccinés. Après avoir reclassé parmi les sujets non vaccinés 55 enfants dits vaccinés mais ne présentant pas de cicatrice de BCG et pour lesquels aucun certificat de vaccination n'était disponible, l'efficacité observée était de 53%. Du fait de la forte incidence de tuberculose observée, ce chiffre traduit une efficacité appréciable du point de vue de la prévention des cas.

L'efficacité semble varier avec le type de maladie. Si l'on considère l'hypertrophie des ganglions lymphatiques hilaires (très fréquemment observée), l'efficacité est faible et dépourvue de signification statistique. Pour les autres types observés, l'efficacité est meilleure. Il faut noter que souvent, l'hypertrophie des ganglions lymphatiques hilaires non compliquée est un signe d'infection et non de maladie. Comme la vaccination par le BCG n'empêche pas l'infection mais empêche la dissémination du bacille via le sang, ce sont les complications plus que l'hypertrophie elle-même qui peuvent servir d'indicateur de l'efficacité de la vaccination. En intégrant aux groupes des cas les sujets atteints d'hypertrophie des ganglions lymphatiques hilaires, on arrive à une baisse trompeuse de l'efficacité observée. En observant ces cas plus longtemps, on aurait eu une estimation plus exacte (et peut-être plus élevée) de l'efficacité. Toutefois, pour des raisons éthiques évidentes, une chimiothérapie a été prescrite dès les premiers signes évoquant une tuberculose. Aucun cas de tuberculose miliaire ni de méningite tuberculeuse n'a été observé.

On n'a pas observé de différence d'efficacité entre les enfants les plus jeunes et ceux qui sont plus âgés. Cela indique que l'effet protecteur de la vaccination par le BCG faite à la naissance ne s'atténue pas au cours des deux ou trois premières années de la vie.

La sensibilité à la tuberculine était faible chez une forte proportion des sujets vaccinés, ce qui indiquerait que la vaccination n'était que faiblement positive. Bien que le rôle de la dose administrée ne soit pas connu, une vaccination à plus forte dose aurait peut-être suscité une meilleure protection.

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