Trial of BCG vaccines in south India for tuberculosis prevention: first report *

TUBERCULOSIS PREVENTION TRIAL [1]

The protective effect of BCG vaccination is being evaluated in a controlled community trial near Madras in south India. After tuberculin and sensitin testing and radiographic and bacteriological examinations, BCG vaccines and placebo were allocated randomly to about 260 000 individuals, of whom 115 000 were definitely tuberculin negative at the time of vaccination. Intensive efforts are being made, by means of regular follow-up surveys, to identify all new cases of tuberculosis occurring in the community. This report presents the findings of the first 7½ years of follow-up. Incidence of infection was high in the study population. However, incidence of bacillary disease was more frequent among initial tuberculin reactors, especially among the older persons, than among non-reactors of whom the majority were in the younger age groups. The distribution of new cases of bacillary tuberculosis among those not infected at intake did not show any evidence of a protective effect of the BCG vaccines.

Although BCG vaccine has been in use for over 50 years, its mode of action—and indeed the immune mechanism in tuberculosis—has remained largely obscure. In particular, it has not been possible to quantify, or even identify, the critical factors that govern the level of protection BCG vaccination can confer to man. That such factors must exist has emerged from the results of controlled field trials, which showed protection to range from none to as much as 80%. Unfortunately, the results of the trials offer only a few pointers, since the trials were independent and factors that are possibly relevant were confounded in the individual designs (*1*).

The following sources of variation may have been important: the vaccines for the different trials were

prepared in different laboratories from cultures that had been propagated for many years and had therefore been subject to mutation and selection of mutants (in fact, the original BCG strain is not, strictly speaking, a "strain" according to present standards, since it was not derived from a single colony but from a whole culture (*2*)); differences in immunogenicity and virulence among the strains used in some of the trials could be demonstrated in experimental animal models, and the potency differences observed in these models were closely associated with the observed differences in protection (*3-6*); and differences in the production methods (concentration, viability) and the dosages. Retrospective analysis of one trial, however, showed that the influence of these latter factors appeared to be fairly marginal for the BCG vaccine concerned (*7*). Thus, the strain could indeed be an important variable. This is also suggested by the fact that, for the trials in which BCG vaccination appeared ineffective (*8-10*), the vaccine had been prepared by the same laboratory. On the other hand, vaccine from this laboratory proved highly effective in another trial (*11*). In a further trial (*12*) two very different vaccinations with BCG and vole bacillus vaccines (the former by injection, the latter by multiple puncture) appeared to give the same level of protection. The actual relevance of the vaccine strain to the protective effect in man therefore remains problematic.

A further factor invoked retrospectively is the presence, in some of the study populations, of sensitization by mycobacteria other than the tubercle bacillus. It has been suggested that such sensitization could be associated with protection against tuberculosis and possibly could mask the protective effect of BCG vaccination. That hypothesis was confirmed in experiments in mice (13) and in guinea pigs (14) in which a variety of saprophytic mycobacteria were shown to induce different levels of protection against virulent challenge, and in which additional vaccination with BCG appeared not to induce a higher level of protection than vaccination with BCG alone. This was borne out in a surveillance programme of naval personnel (15). In the trials in which BCG vaccination proved ineffective, or had a low effectiveness, the presence of nonspecific sensitivity was indeed demonstrated, but detailed quantitative analyses showed that nonspecific sensitivity alone could not have masked completely the effect of a vaccine that would have had a high efficacy in a nonsensitized population (1, 16). Also, in one trial in which a modest protection was observed this applied equally to the populations with and without low grade sensitivity (17).

Finally it should be mentioned that one factor, the presence or absence of tuberculous infection in the trial subjects was, in fact, considered, in relation to selection of subjects, in all the trials. However, in view of the very rationale for vaccination against tuberculosis, this factor was implicitly assumed to play such an important role that no attempts were made to investigate it further; infected subjects have invariably been excluded from vaccination trials.

Neither the empirical findings of the field trials nor other epidemiological observations gave any indication of further relevant factors, but lack of detailed epidemiological knowledge could well have been important in this respect. The apparently conflicting trial results, as well as the fact that the vaccines employed in the trials cannot be reproduced, called for further and more systematic research. To some extent this had become easier because of the technical progress made meanwhile in the preparation of BCG vaccine. Freeze-drying techniques had been developed that made it possible to prepare a stable product from any BCG strain, and to maintain the strains as seed lots without the risk of further genotypic alterations (18). Accordingly there was a need to undertake further field trials with vaccines prepared from different seed lots and in different dosages, and to conduct these trials in populations where nonspecific tuberculin sensitiv-

ity was present and in others where it was absent. The incidence of tuberculosis in the study populations should be fairly high, and BCG vaccination should not be a current public health measure. A trial satisfying most of these conditions was organized in south India by the Indian Council of Medical Research (ICMR), in cooperation with the World Health Organization and the Center for Disease Control, US Public Health Service, in a population where nonspecific tuberculin sensitivity was highly prevalent. Unfortunately, a contrasting area in which nonspecific tuberculin sensitivity was of low prevalence, or even absent, could not be identified in India, at that time.

MATERIALS AND METHODS

Trial location and population

The trial area included a total population of about 360 000 persons in 209 villages and 1 town located to the west of Madras city, the town being 40 km from Madras. The entire resident population (except for children under 1 month old) was eligible for inclusion in the trial. Since it was considered that BCG vaccination might increase the specific immunity in people whose naturally acquired immunity (from virulent infection) might have waned in the course of time, persons classified as infected on the basis of the tuberculin test were not excluded from vaccination.

Study design

The design may be described as a 3×2 factorial, the first factor being the vaccine strain (and placebo), the second the dosage. For practical reasons only two seed lots—the French strain (seed lot 1173 P2) and the Danish strain (seed lot 1331)—were included in the trial and these were selected on the basis of their comparatively favourable effects in experimental models (19, 20).

It should be noted that the French strain is in use in over 20 BCG production laboratories, and the Danish strain in several other laboratories, including the one in India. For the placebo preparation, dextran was freeze-dried in ampoules to form a powder of the same appearance as dried BCG vaccine. Since this preparation is innocuous, however, it does not cause the same kind of scar as BCG. The vaccine was administered at the usual strength (1 mg/ml) and one-tenth of this strength (0.1 mg/ml). The variations in dosage administered in most BCG vaccination programmes, including those due

to variations in the viability of the vaccine and in the amount injected, have usually been well within this range.

Vaccines and placebo preparation

Three shipments of vaccines and placebo were supplied by the State Serum Institute, Copenhagen, and three batches were supplied by the BCG Vaccine Laboratory, Guindy, Madras. The ampoules (10 ml in Copenhagen, 5 ml in Madras) were packed in boxes of three. Each (coded) box contained 1 ampoule of strong vaccine, 1 ampoule of weak vaccine of the same strain, and 1 ampoule of placebo. The ampoules in each box were randomly coded (1, 2, and 3), and the codes were kept in the production laboratories, by WHO in Geneva, and by the ICMR in New Delhi; they were not available to the project staff.

Intake

Intake started in July 1968 and was completed in March 1971. The intake procedure consisted of a complete house-to-house census to record each person's name, relationship to the head of the household, age, sex, occupation, etc. After the census, the persons were directed to a conveniently located examination centre. At this centre, the identification was verified and the person's left shoulder was examined for the presence of a BCG scar. Persons aged 1 year or more were tested with 3 IU of PPD-S and 10 "units" of PPD-B (intracellularin) and the reactions were read in most cases after 72 hours. Subjects over 1 month old were vaccinated by intradermal injection of 0.1 ml of vaccine (or placebo), after which a fingerprint (or for small children a palmprint) was taken. X-ray examination was offered to all persons aged 10 years or more and the X-ray films were examined independently by two readers. If on the basis of an X-ray reading tuberculosis was suspected, "on-the-spot" and "overnight" sputum samples were collected. The samples were examined by fluorescence microscopy and, after decontamination and concentration, were cultured on two Löwenstein-Jensen slopes. Cultures were classified as Mycobacterium tuberculosis on the basis of both the morphological characteristics of the colonies and the niacin test and other identification tests, such as growth characteristics at 25°C and drug sensitivity to 4-nitrobenzoic acid. The presence of drug resistance to isoniazid and streptomycin was also examined in all cultures.

Follow-up

The survey methods used at the time of intake were repeated at 2½-year intervals, X-ray examination being offered to all subjects 5 years of age and over. During the second resurvey (i.e., between 2½ and 5 years after intake) only those persons with reactions to PPD-S of less than 16 mm at intake and those considered at high risk in view of the previous examinations could be examined. However, in a random sample of one-third of all villages included in the study, all individuals aged 5 years and above were examined at each resurvey according to the criteria adopted for the first resurvey.

Two or three times between surveys every village was visited and all persons who had had a suspect X-ray shadow at the previous survey, or who were absent at the previous survey, were offered X-ray examination. Also persons with cough or chest pain were invited to submit to an examination. A tuberculosis clinic was set up in the central town, and an
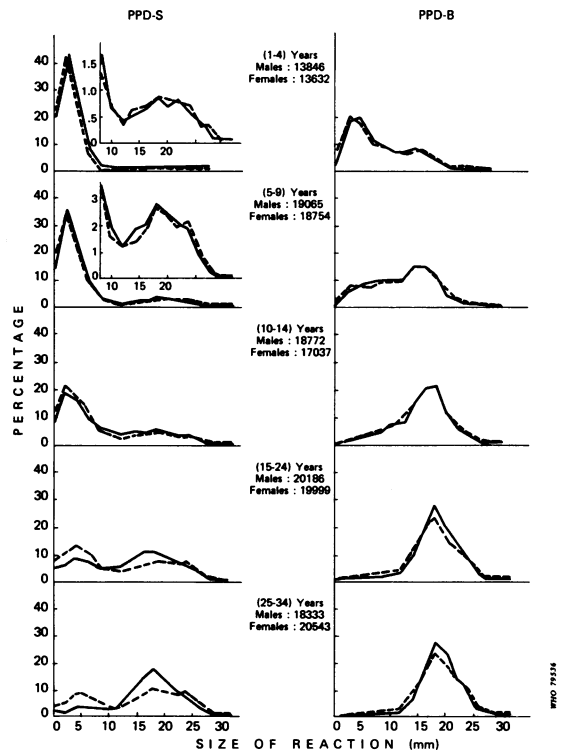

Fig. 1. Percentage distribution of reactions to PPD-S and PPD-B at intake among the age groups up to 34 years of age. For PPD-S, the percentage distribution of the larger reactions for the two youngest age groups is shown on a larger scale in the insets. Solid lines —males; dashed lines—females.

X-ray unit visited the ten rural health institutions in the study area every 2–4 weeks. The diagnostic procedures were the same as during the intake. Cases diagnosed were offered domiciliary chemotherapy.

A 2% random sample of the population was retested at 2½ months, another 5% were retested at 2½ years, and a further 85% were retested at 4 years after vaccination. Retests were done with 3 IU of PPD-S only.

RESULTS

Prevalence of infection and disease

The main findings of the intake examinations are summarized in Table 1. The classification of the study population as infected or noninfected on the basis of PPD-S and PPD-B testing proved impossible (21). The distribution of reaction sizes to PPD-S, however, showed a fairly clear antimode, in the lower age groups, at around 12 mm (see Fig. 1) and persons with a reaction of 12 mm or larger may therefore be considered positive (infected). Indeed, among over 1000 patients with at least two positive cultures only 1.4% had reactions to PPD-S smaller than 12 mm. At the chosen threshold, therefore, the test may be considered highly sensitive. Those with reactions of 0–7 mm at intake have been considered as definitely not infected.

The sputum samples collected were examined by smear (fluorescence microscopy) and by culture. In comparison with culture, the smear examination appeared inferior, especially for the samples that showed scanty growth on culture: one-third of the patients were positive on culture only. On the other hand, 22% of the patients were positive on smear only, but on most specimens only 1–3 bacilli were seen on the entire smear, and almost always only one of the smears was positive in this way. Whether such cases positive on smear only, can be considered as bacillary cases, is doubtful. Therefore, only the culture results have been considered pathognomonic.

A high proportion of the patients were culture-positive on one specimen only. In these cases there were very often only a few colonies. While there must have been many true bacteriologically positive (perhaps early) cases of tuberculosis among these, some false cases (for example, contaminated samples) may have been included. Reproducibility of cultures as well as confirmation by other techniques was distinctly higher among cases positive on both culture and smear, than among cases positive on culture only. Cases positive on one culture only had certain features that were markedly different from those positive on two or more cultures. For this reason the results are presented separately for those

Table 1. Characteristics of the study population at intake

| | | \multicolumn{8}{c}{Age (years)} | Total |
		0–4[a]	5–14	15–24	25–34	35–44	45–54	55–64	≥	
No. registered	M	24 074	46 494	29 905	28 384	22 161	16 691	10 467	6 093	184 269
	F	23 880	43 773	31 585	28 999	21 040	16 041	9 887	5 372	180 550
No. examined[b] and vaccinated at intake	M	16 199	38 369	21 289	19 519	15 700	12 238	7 739	3 959	135 012
	F	16 136	36 093	19 988	20 259	16 336	12 088	6 749	2 511	130 160
Proportion (%) tuberculin positive (≥ 12 mm to 3 IU of PPD-S)	M	4.9[c]	23.5	62.0	81.8	85.2	85.5	82.6	79.9	54.0
	F	5.3[c]	21.3	48.4	64.0	71.6	73.7	72.4	72.8	45.8
Proportion (per 10 000) culture positive (at least 2 specimens)	M		1[d]	33	115	179	213	219	200	111
	F		2[d]	11	25	40	39	38	28	23
Proportion (per 10 000) culture positive (one specimen only)	M		3[d]	13	39	91	107	145	192	60
	F		2[d]	10	17	29	42	40	40	20
Proportion (per 10 000) culture negative, but X-ray indicating active tuberculosis possible or probable	M		31[d]	47	107	245	379	478	703	189
	F		34[d]	34	62	111	160	262	435	98

[a] Children less than 1 month old are excluded.

[b] Including children under 10 years of age, who were not eligible for X-ray examination, and children under 1 year of age, who were not eligible for tuberculin testing.

[c] 1–4 years.

[d] 10–14 years.

culture positive on two specimens and on one specimen.

As regards the X-ray examination, the agreement between the readers on active tuberculosis being possible or probable was not more than 47%. A third reader examined all the cases so classified by one reader only. Only cases confirmed by two of the three readers are included in the figures given (Table 1).

Incidence of infection and disease

Repeat tuberculin tests were given to assess the post-vaccination tuberculin sensitivity at 2½ months, 2½ years, and 4 years after intake. At 4 years, when the sample was the largest and, especially for the 1–4-year age group, the observed incidence of infection in the control group makes it possible to estimate the risk of infection during this period (Table 2). A person was considered to be newly infected if he was uninfected at intake (0–7 mm to 3 IU of PPD-S) and if his reaction to the same test was at least 10 mm larger 4 years later. The average annual risk of infection appears to have

Table 2. Incidence and risk of infection in the placebo group during the first four years

	Age (years) at time of survey		
	1–4	5–9	10–14
No. with reaction of 0–7 mm at intake	4 518	5 467	3 231
No. with reaction after 4 years ⩾10 mm larger than at intake	486	908	690
Average annual risk of infection (%)	2.8	4.4	5.8

varied with age at intake. Although the study population was large, these estimates must be considered as rough indications only, since in the population concerned the test used was not sufficiently specific. Nevertheless, infection with *M. tuberculosis* in the trial area appears to have been at least as common as in other parts of India, if not more so.

The incidence of pulmonary tuberculosis confirmed by culture during the first follow-up round is given in Table 3. Relative to the population examined at intake, the average annual incidence of disease was 3 per 1000 in males and 1 per 1000 in

Table 3. Culture-positive cases found during the first follow-up by age, tuberculin reaction, and X-ray result at intake

Tuberculin reaction (mm) at intake	X-ray result at intake	Age group at intake (years)								Total
		0–4	5–14	15–24	25–34	35–44	45–54	55–64	⩾65	
Culture-positive (at least two specimens)										
0–7	normal	4	2	2	4	1	1	2	1	17
	other			1		2		2	1	6
8–11	normal			2	4	3				9
	other				1		2	2	2	7
12–15	normal		1	1	6	5	7	2	1	23
	other			1	2	10	11	4	6	34
⩾16	normal	1	10	37	51	63	48	28	12	250
	other		2	30	80	140	150	106	54	562
Total	normal	5	13	42	65	72	56	32	14	299
	other		2	32	83	152	163	114	63	609
Culture-positive (one specimen only)										
0–7	normal	4	9	1	1	1		1	2	19
	other		2	1	1	3	2		1	10
8–11	normal								2	2
	other				1			1	1	3
12–15	normal			3	2	2	1	1	3	12
	other			1	2	1	4	4	4	16
⩾16	normal		5	17	32	17	20	15	7	113
	other		1	16	38	53	58	52	30	248
Total	normal	4	14	21	35	20	21	17	14	146
	other		3	18	42	57	64	57	36	277

females. Of particular interest in connexion with the effect of BCG vaccination is the distribution of the cases found according to the tuberculin reaction at intake. Among those with a reaction of 0–7 mm the average annual incidence of cases positive on at least 1 specimen was 0.2 per 1000, among those with a reaction of 8–11 mm 0.4 per 1000, among those with 12–15 mm 1.5 per 1000, and among those with a reaction of 16 mm or more 4.5 per 1000. Thus, in those who were most probably not infected at intake the incidence of disease was surprisingly low (even when considering that two-thirds were vaccinated (see Table 4).

BCG-induced tuberculin sensitivity

The level of tuberculin sensitivity induced by BCG vaccination is an indication of the quality of the vaccination since this level is known to be correlated with the dose of (live) vaccine actually introduced into the skin (22). Moreover, tuberculin sensitivity,

as it reflects cell-mediated immunity, may be related to the protection afforded (23).

It appeared that there were no significant differences between the various batches of vaccine used. The observations in the age groups 0–4 and 5–9 years (at intake) for all the strong vaccines are therefore compared with the placebo (see Fig. 2) to illustrate the level of tuberculin sensitivity induced and its development with time. At 2½ months after vaccination, the vaccinated persons in both groups showed a unimodal, almost normal, distribution with a mean reaction size of 16 mm. After 2½ and 4 years this pattern had changed considerably and the reactions were much smaller. Still, the average level of sensitivity remained considerably higher than in the control group. Tuberculin sensitivity apparently waned during the first few years following vaccination but then remained at the same level. It should be noted that in this evaluation any boosting of tuberculin sensitivity as a result of repeated testing (24) was avoided by testing different sample populations on each occasion.
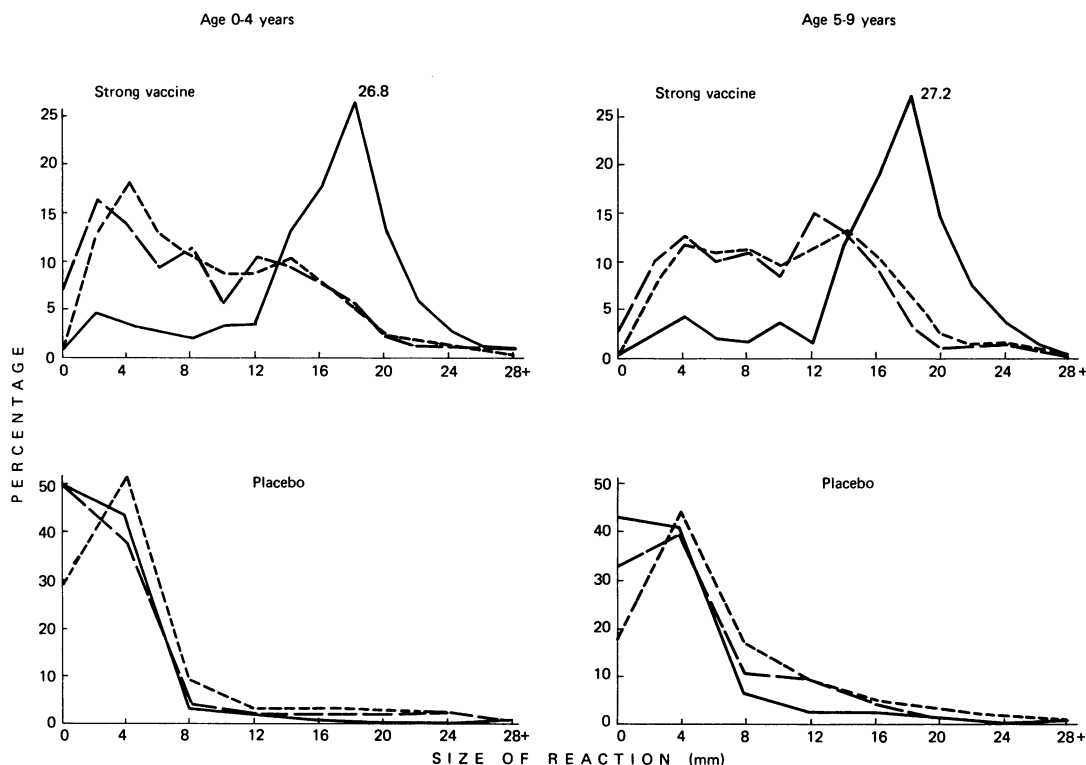

Fig. 2. Percentage distribution of tuberculin reactions at various intervals after vaccination in persons with initial reactions of 0-7 mm. Solid lines—2½ months; broken line—2½ years; short dashes—4 years.

Incidence of tuberculosis among the vaccinated and the controls

The numbers of new cases detected during the first 7½ years of the follow-up, separately for the vaccinated and the control groups and for different levels of tuberculin (PPD-S) sensitivity at intake, are given in Table 4. Exact relative incidence figures are not yet available, but it may be taken that the denominators for the vaccine groups and the placebo group are the same. Thus it is clear at a glance that BCG vaccination at this stage had had no effect. Under these circumstances the significance of the differences between vaccine strains and dosages can scarcely be examined. The very remote possibility of one strain being associated with a protective and the one other with a harmful effect was examined. As no such difference was observed the results for both strains have been combined.

Table 4. Number of new cases with at least two culture-positive specimens (no. with only one in brackets) detected during 7½ years of follow-up according to initial tuberculin reaction and vaccine group

Tuberculin reaction at intake (mm)	Vaccine 0.1 mg/ml	Vaccine 0.01 mg/ml	Placebo	Total
0–7	37 (22)	37 (28)	28 (19)	102 (69)
8–11	14 (4)	17 (3)	14 (5)	45 (12)
12–15	40 (20)	34 (13)	38 (8)	112 (41)
≥16ᵃ	259 (90)	257 (91)	287 (82)	803 (263)

ᵃ This group was not eligible for active follow-up during the 2nd and 3rd resurveys.

It is seen that in all groups the large majority of the cases occurred among those already infected at intake. In this connexion it should be noted that those with a reaction of 16 mm or larger were not eligible for active follow-up during the later rounds. (For this reason column totals have been omitted.)

DISCUSSION

The results of the trial reported here show that BCG did not give any protection during the first 7½ years after vaccination. Details of eight BCG trials, including the present one, in which the protection observed varied from 0 to 80 %, are given in Table 5. BCG vaccination has been the subject of controversy throughout its more than 50-year history. With this new result at hand, it is perhaps appropriate to discuss some of the hypotheses that may explain the different findings.

Table 5. Protection obtained in eight BCG trials

Trial and subjects	Duration of observation (years)	Percentage protection	Reference
North American Indians	9-11	80	25
Chicago: infants	12-23	75	11
Georgia: schoolchildren	20	none	8
Puerto Rico: population under 20 years of age	5½-7½	31	26
Georgia and Alabama: general population	14	14	10
Great Britain: schoolchildren	15	78	12
Madanapalle, south India: general population	9-14	31	27
Chingleput, south India: general population	7½	none	present trial

There is no doubt that BCG strains mutate in terms of colony morphology and in terms of antigenicity. However, at least for the Danish strain, the evidence indicates that the vaccine strains used in these studies had not mutated from the original protective strains. The Danish strain used in India was the same as that used earlier in Britain (*12*), which did give substantial protection, and three circumstances favour the hypothesis that there was not any genetic change in the strain between 1952 and 1960 (when the strain was made into a stable seed-lot). First, every year for the last 30 years, the allergenicity of the Danish vaccine has been monitored in Danish schoolchildren and there has not been any change over this period. Second, the methods used to propagate this strain between 1947 and 1960 were conservative, as advocated by Calmette. Third, comparison of vaccines prepared from the seed-lot with vaccines prepared from cultures maintained by culture transfers from 1958 to 1965, did not reveal any differences in morphology, antigenicity, or virulence in animals, or in allergenicity in children. For the French strain, the evidence is less clear. There was a mutation in pigmentation in the late 1950s, though the French workers feel that they succeeded in saving the original strain by back-selection. In the recent experiment by D. W. Smith and coworkers (personal communication, 1979), the French strain protected guinea pigs well, though significantly less than the Danish strain. Further evidence on this point would be welcome. Thus, there is circumstantial evidence that the strains used here were "genuine" BCG. A meeting of chiefs of

quality control laboratories, held in Copenhagen in February 1978, concluded that the vaccines used in the trial were of good quality.

The methods and materials of the study were scrutinized at a meeting of experts held in Madras in 1977, and it was concluded that there were not any apparent flaws in the procedures followed in the study. With the very involved code for the vaccine ampoules it is conceivable that true protection might have been masked by labelling or recording errors. However, since a blind reading of vaccination lesions in a very large proportion of the population tallied with the records of the codes in 99.8 % of cases, such recording errors cannot have influenced the results.

Since the trial was carried out in an area with a high prevalence of nonspecific sensitivity, it might be expected that sensitization by "atypical" mycobacteria would result in an apparent reduction of the effect of BCG. Had some protection been observed in the present trial, this question could have been examined; with zero protection this was not possible. However, the hypothesis has once been tested, retrospectively: in the study in Puerto Rico, vaccine and placebo were allocated irrespective of the reaction to a high-dose test, and it turned out that there was the same low protection (31 %) in those positive and those negative to the high-dose test (17, 28).

The lack of protection observed in this study could possibly be explained by the hypothesis that the vaccinated individuals were at increased risk of developing tuberculosis if they were infected within 3 weeks after vaccination, i.e., before the manifestation of cell-mediated immunity. This, however, is unlikely and not borne out by the findings.

Vaccines similar to the ones used in the present study have given a high protection in some (though not necessarily all) past studies. The lack of protection in the present study seems to be associated with a peculiar epidemiological situation. Our forecast of the incidence of tuberculosis among persons tuberculin-negative at the time of vaccination was based on available knowledge of tuberculosis epidemiology, and in particular on the results of the "longitudinal survey" conducted from 1960 onwards in Bangalore district, Karnataka, by the National Tuberculosis Institute (29). During the first resurvey of that study, after 18 months, the annual incidence of new bacillary cases among those with a reaction of 0–9 mm to RT 23 (1 unit, with Tween 80) was estimated at 58 per 100 000 while in the present study among those reacting with 0–7 mm to PPD-S 3IU, it was only 25 per 100 000. Though the data are not strictly comparable, the very much lower risk among non-reactors in the present study, in relation to the considerably higher risk among those defined as infected at intake, is a very striking finding.

It appears, therefore, that while the infection rate is high in this study population and possibly not declining, newly infected persons develop disease less frequently. Tuberculosis is highly prevalent, but only among the middle-aged and especially elderly men, individuals who must have been infected many years, even decades, ago. It is possible that it is not the primary infection but rather superinfection in the host already allergic from a previous infection that is the cause of the "adult" type of lung tuberculosis. Could it be that BCG protects against endogenous reactivation but not against exogenous reinfection? This requires further investigation. The present project offers a chance of testing this hypothesis directly.

A local phenomenon that may be of relevance is the frequency of strains of *M. tuberculosis* that are of very low virulence in the guinea pig. This phenomenon was exhaustively studied by Mitchison and coworkers (see 30). Mitchison found these low-virulence strains to be susceptible to hydrogen peroxide, though they tended to be catalase-positive. Nothing seems to be known, however, about the epidemiological significance of these strains. They have been isolated from previously untreated patients admitted to the Tuberculosis Chemotherapy Centre, Madras (so they are presumably not always avirulent in man) and they were niacin-positive and isoniazid-sensitive. Evidence from elsewhere in India is scanty but compatible with the existence of these low-virulence strains in other parts of the country. Work is now underway in this project to study the distribution of such strains, especially in regard to age distribution, infection history, and fate of the patients. While there is as yet no indication of an association between the prevalence of these strains and the BCG results, it nevertheless seems worth while to investigate this phenomenon.

In conclusion, the present study has shown that the BCG did not give any protection against the development of bacillary disease. Protection afforded to individuals against development of active disease other than bacillary forms remains to be studied. It should be pointed out that the present results may not be extrapolated to infants, since infant tuberculosis was not observed in the trial. Information on the effect of BCG vaccination in infants is scarce, and additional data are badly needed.

RÉSUMÉ

ESSAI DE VACCINS BCG DANS LE SUD DE L'INDE POUR LA PRÉVENTION DE LA TUBERCULOSE: PREMIER RAPPORT

L'effet protecteur de la vaccination par le BCG est actuellement évalué dans le cadre d'un essai contrôlé au niveau de la communauté près de Madras dans le sud de l'Inde. Dans cet essai, après exécution d'épreuves à la tuberculine et d'épreuves aux sensitines ainsi que d'examens radiologiques et bactériologiques, des vaccins BCG lyophilisés préparés à partir de deux souches, à savoir 1331 et 1173P2, et des placebos ont été répartis au hasard entre environ 260 000 individus, dont 115 000 étaient certainement tuberculino-négatifs lors de la vaccination. Deux doses (0,1 mg et 0,01 mg) de BCG ont été utilisées. On s'emploie intensivement, au moyen d'enquêtes suivies régulières, à repérer tous les nouveaux cas de tuberculose au sein de la communauté. Le rapport présente les observations faites au cours des sept premières années et demie de ces enquêtes. L'incidence de l'infection est élevée dans la population soumise à l'enquête. Toutefois, l'incidence de la maladie bacillaire est plus fréquente chez les sujets ayant réagi positivement à la tuberculine au début de l'essai, notamment parmi les personnes âgées, que chez les sujets à réaction négative, qui sont des jeunes en majorité. La répartition des cas nouveaux de tuberculose bacillaire parmi ceux qui n'étaient pas infectés lors de l'inoculation n'apporte en aucune façon la preuve de l'effet protecteur des vaccins BCG.

REFERENCES

1. TEN DAM, H. G. ET AL. *Bulletin of the World Health Organization,* **54**: 255 (1976).
2. FRAPPIER, A. ET AL. In: *Immunization in tuberculosis,* Bethesda, Center for Disease Control, 1971, p. 157 (DHEW Publication No. (NIH) 72-78).
3. DUBOS, R. J. & PIERCE, C. H. *American review of tuberculosis and pulmonary diseases,* **74**: 699 (1956).
4. WILLIS, H. S. ET AL. *American journal of the medical sciences,* **240**: 137 (1960).
5. WILLIS, H. S. & VANDIVIERE, M. R. *American review of respiratory diseases,* **84**: 288 (1961).
6. JESPERSEN, A. *The potency of BCG determined on animals.* Copenhagen, Statens Seruminstitut, 1971.
7. HART, P. D'ARCY ET AL. *Tubercle,* **48**: 201 (1967).
8. COMSTOCK, G. W. & WEBSTER, R. G. *American review of respiratory diseases,* **100**: 839 (1969).
9. BETTAG, O. L. ET AL. *Diseases of the chest,* **45**: 503 (1964).
10. COMSTOCK, G. W. & PALMER, C. E. *American review of respiratory diseases,* **93**: 171 (1966).
11. ROSENTHAL, S. R. ET AL. *Pediatrics,* **28**: 622 (1961).
12. BRITISH MEDICAL RESEARCH COUNCIL. *Bulletin of the World Health Organization,* **46**: 381 (1972).
13. YOUMANS, G. P. ET AL. *American review of respiratory diseases,* **83**: 403 (1961).
14. PALMER, C. E. & LONG, M. W. *American review of respiratory diseases,* **94**: 553 (1966).
15. EDWARDS, L. B. & PALMER, C. E. *Annals of the New York Academy of Sciences,* **154**: 40 (1968).
16. HART, P. D'ARCY. *British medical journal,* **1**: 587 (1967).
17. COMSTOCK, G. W. & EDWARDS, P. Q. *Scandinavian journal of respiratory diseases,* **53**: 207 (1972).
18. WHO Expert Committee on Biological Standardization. Eighteenth Report, Geneva, 1966 (WHO Technical Report Series, No. 329).
19. VALLISHAYEE, R. S. ET AL. *Bulletin of the World Health Organization,* **51**: 489 (1974).
20. LADEFOGED, A. ET AL. *Bulletin of the World Health Organization,* **53**: 435 (1976).
21. RAJ NARAIN ET AL. *Indian journal of medical research,* **62**: 1596 (1978).
22. EDWARDS, L. B. ET AL. *BCG vaccination.* Geneva, World Health Organization, 1953 (WHO Monograph Series, No. 12).
23. MACKANESS, G. B. *American review of respiratory diseases,* **97**: 234 (1968).
24. GULD, J. ET AL. *Bulletin of the World Health Organization,* **39**: 829 (1968).
25. STEIN, S. C. & ARONSON, J. D. *American review of tuberculosis and pulmonary diseases,* **68**: 695 (1953).
26. PALMER, C. E. ET AL. *American review of tuberculosis and pulmonary diseases,* **77**: 877 (1958).
27. FRIMODT MØLLER, J. ET AL. *Indian journal of tuberculosis,* **15**: 40 (1968).
28. COMSTOCK, G. W. ET AL. *American journal of public health,* **64**: 283 (1974).
29. NATIONAL TUBERCULOSIS INSTITUTE, BANGALORE. *Bulletin of the World Health Organization,* **51**: 473 (1974).
30. MITCHISON, D. A. *Bulletin of the International Union against Tuberculosis,* **35**: 287 (1964).