BCG AND VOLE-BACILLUS VACCINES IN THE PREVENTION OF TUBERCULOSIS IN ADOLESCENTS

SUMMARY OF FIRST (PROGRESS) REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS VACCINES CLINICAL TRIALS COMMITTEE*

In July 1949 the Medical Research Council, aware that a clinical trial of the BCG (Bacille Calmette-Guérin) and vole-bacillus vaccines was needed to provide essential information, appointed this committee to plan and direct an investigation. The following is the first report of this trial, which is still in progress, and presents preliminary findings at a time when every participant has been observed for 2½ years, and a few for 4 years. Since the trial is still in progress and the record cards are in continual use the statistics in this first report are based on representative samples of the record cards, except for the cases of tuberculosis amongst the participants, which have been completely enumerated and not estimated from samples.

The trial is designed to test the degree and duration of protection afforded by each of the two vaccines in adolescence, since the incidence and mortality in tuberculosis begin to rise at about the age of 15 from the low levels of childhood. Random vaccinated groups are to be compared with similar random unvaccinated groups and the participants are being followed up intensively for several years at least.

The Intake. The mass clinical test involved 56,700 boys and girls between 14 and 15½ years of age (mostly 14½-15) collected in 1950-1952 during their final year at 'secondary modern schools'. Of these, 23,400 were at schools at Birmingham, 18,800 at Manchester and 14,500 in the north of London—all large, densely-populated, industrialized areas.

Exclusions. The original intake of volunteers numbered 61,400, and the numbers were reduced by the following screening procedures:

1. Every child known to have tuberculosis in his immediate family or to have been in recent contact with a case at home was excluded.

2. A 35-mm. radiograph of the chest was taken of every child, and if any unusual appearance was noted the child was recalled for a full-plate chest radiograph. All children found or suspected to have any form of tuberculosis (apart from calcification of primary type) were excluded.

About 1,800 children were excluded on one or other of these grounds, 2,500 because they had not completed the initial radiographic examination and tuberculin tests, and 400 more for other reasons.

Classification by Tuberculin Test.

A Mantoux test (on the forearm) was then made of every entrant with 3·3 tuberculin units (3 TU), using 0·1 ml. of 1/3,000 OT; the greatest diameter of palpable infiltration at the end of 72 hours was recorded in mm. If there were no infiltration or if its diameter was less than 5 mm. the reaction to 3 TU was regarded as negative and another intracutaneous test was made on the same forearm with 100 TU, using 0·1 ml. of 1/100 OT; the greatest diameter of infiltration at the end of 72 hours was again recorded. Children with no infiltration, or with a diameter of infiltration less than 5 mm., at the second tuberculin test, were regarded as negative reactors to 100 TU.

The positive reactions numbered 22,600 (40%) 16,000 (28%) reacting to the weaker tuberculin (3 TU) and 6,600 (12%) to the stronger (100 TU) only.

The Vaccination. The negative reactors (60%) were divided into 3 strictly random* groups, which were respectively left unvaccinated (13,300), vaccinated with BCG (14,100), and vaccinated with vole bacillus (6,700). The dose of BCG (State Serum Institute, Copenhagen) was 0·1 ml. of vaccine (0·75 mg. of semi-dried weight bacilli per ml.) injected intracutaneously, and the vole-bacillus (Lister Institute, 2 mg. of wet weight bacilli per ml.) was introduced into the skin by a multiple-puncture instrument with 40 needles, projecting 2 mm. on release. The boys were vaccinated in the left deltoid region and the girls in the upper and outer part of the left thigh. The vaccination was carried out immediately after the result of the test with 100 TU had been read.

Second Examination. To observe the immediate effects of vaccination it was found possible in their last term at school to re-examine the children who entered the test in 1950 and 1951 (but, with a few exceptions, not the other participants). The examination included (*a*) a 35 mm. chest radiograph and, if indicated, a full-plate one, (*b*) tuberculin tests (as described above) except in those who had given strongly positive reactions at the first test, (*c*) the measurement of each BCG vaccination reaction, and the classification of each vole-bacillus reaction, and (d) the recording of local complications of vaccination.

Follow-up. Each participant was approached 3 times in the period of approximately 14 months after leaving school by the following channels:

(1) An enquiry form by post at approximately 4 months (repeated more than once if necessary. 77% returned at least one postal enquiry form within 18 months of their entry to the trial.)

(2) A visit from a local health visitor at approximately 10 months, making the same enquiries. (76% were thus visited at least once within 18 months of their entry to the trial.)

(3) At approximately 14 months (10-18 months) participants, now nearly all in employment, were invited to an examination by a mobile clinic including the same 4 items as the 'second examination' (see above) except that *every* participant was expected to undergo the Mantoux test(s). Those who did not attend were invited to do so

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* From the full report in the *British Medical Journal* of 25 February 1956 (p. 413). Members of the Committee: Dr. P. D'Arcy Hart (chairman), Sir John Charles, Prof. R. Cruickshank, Dr. Marc Daniels (secretary until his death in 1953), Dr. W. Pointon Dick (resigned in 1951), Dr. J. E. Geddes, Prof. A. Bradford Hill, Sir Wilson Jameson, Dr. V. H. Springett, Dr. Ian Sutherland, Dr. A. Q. Wells, Dr. G. S. Wilson, Dr. T. M. Pollock (secretary).

* except that all the London children who were vaccinated, and for a short time all the Birmingham and Manchester vaccinees, received the BCG vaccine; and for a short time all the Birmingham and Manchester vaccinees received vole-bacillus vaccine.

when the team visited the district again later. (52% had a chest radiograph taken after leaving school, within 18 months of their entry to the test, and not less than 74% within 2 years of their entry.)

Within 18 months of their entry to the test 94% of the participants had been contacted either by return of a postal enquiry form, by interview with a health visitor, or by the taking of a chest radiograph.

The same cycle of enquiry and examination has been repeated in each subsequent 14-month period. Information has also been made available from local tuberculosis notification lists and local chest clinics. When participants have moved to other parts of the country (or, in a few cases, emigrated) postal enquiries have been sent them annually and arrangements made for annual X-ray examination and, if possible, tuberculin tests.

From these and other sources the records available for each case consisted of periodic radiographs, and the results of clinical examinations by one of the unit physicians or by other physicians, and of bacteriological or pathological examinations. Histological specimens were assessed by the National Institute of Medical Research. In cases of definite or suspected tuberculosis in BCG-vaccinated participants any cultures growing acid-fast bacilli were examined at Colindale for type, pathogenicity, etc. to exclude the possibility that the infecting organism was BCG itself. Similar cultures from vole-bacillus-vaccinated participants were examined at Oxford.

Grouping of Participants. For the purpose of the ensuing analyses, the participants were classified on entry to the trial into the following 5 groups, according to the result of tuberculin tests at the first examination and according as BCG vaccination or vole-bacillus vaccination or no vaccination was applied (see above):

1. Negative on entry (to 100 TU) and left unvaccinated	23%
2. Negative on entry (to 100 TU) and then given BCG vaccine	25%
3. Negative on entry (to 100 TU) and then given vole-bacillus vaccine	12%
4. Positive on entry to 3 TU and left unvaccinated	28%
5. Positive on entry to 100 TU (but negative to 3 TU) and left unvaccinated	12%
	100%

Deaths of Participants. The number of participants known to have died within 2½ years of entering the trial was 38. None of their deaths was due to any form of tuberculosis. The principal causes of death were accidents (13), malignant disease (7) and pneumonia (3). There appear to be no more than chance differences between the mortalities in the 5 groups.

Complications of Vaccination. A few cases of regional adenitis with cold abscess formation, following both BCG and vole-bacillus vaccination, were brought to the notice of the teams, but no evidence that this complication was common. At the second examination at school very few complications, with either vaccine, were seen; a few cases of delayed healing of the vaccination, with shallow ulceration, were noted; the regional glands were not examined as a routine measure. Certain other complications discovered later are described below.

CONVERSION TO TUBERCULIN-POSITIVITY FOLLOWING VACCINATION

Table I* gives the results of the tuberculin tests at the second examination at school (based on representative samples). The findings in the negative unvaccinated group illustrate the effect of natural infection with tubercle bacilli in the 3-5 months between the two examinations at school (coupled with variations inherent in the performance of the tuberculin test). At the second examination only 0·4% of these children were positive to 3 TU and a further 53% were positive to 100 TU only (Table I, Section A). In contrast, 85·8% of the BCG-vaccinated group were positive to 3 TU and a further 13·8% to 100 TU only, representing a total of 99·6%. From Section B of Table I it will be seen that 59·8% in the vole-bacillus-vaccinated group were positive to 3 TU and a further 34·6% to 100 TU only, giving a total of 94·4% converted. It was found that the earlier batches of vole-bacillus vaccine were below standard strength; when this vaccine was brought up to standard in September 1951 the percentages converted were almost identical with those for BCG vaccine.

Size of Reaction. The average diametres of BCG vaccination reactions at the second examination at school were 8·1 mm. for boys (on the arm) and 9·9 mm. for girls (on the thigh).

THE CASES OF TUBERCULOSIS

All the cases, definite and suspected, of tuberculosis were reviewed by an independent assessor who was unaware of the results of tuberculin tests and whether vaccination had been performed. It fell to the assessor also to distinguish between cases of tuberculosis present at the time of entry to the trial and those arising after entry, and to note the date when the disease first became manifest (e.g. when the first abnormal radiograph was taken). The latter date may be a considerable time after the true, but unknown, date of onset of the disease.

Cases of Tuberculosis present on Entry to the Trial

Besides the children excluded from the trial because they were found at the first examination at school to be suffering from definite or suspected tuberculosis, a further 85 cases discovered after the 56,700 participants had completed the first examination and entered the trial were adjudged by the independent assessor to have started before entry. These should not have been included in the trial at the first and were therefore excluded on discovery and are excluded from Tables I and II. (In 67 of the 85 cases the radiograph taken on entry showed on re-scrutiny appearances indicative of tuberculosis; in 14 more—13 of them non-pulmonary—symptoms were present before the participant entered the trial. The report states the reasons why the remaining 4 cases were adjudged by the assessor to have been present at the time of entry; these 4 children had—unknown to the assessor—all given a positive reaction to tuberculin on entry.)

* In the original report it is numbered as Table III.

TABLE I. PERCENTAGES OF PARTICIPANTS, IN THE NEGATIVE UNVACCINATED AND IN THE TWO VACCINATED GROUPS, WHO HAD POSITIVE TUBERCULIN REACTIONS AT THE SECOND EXAMINATION AT SCHOOL (ESTIMATES BASED ON REPRESENTATIVE SAMPLES OF PARTICIPANTS).

Section	*Skin-test and Vaccination Group (On Entry to the Trial)*	*At the Second Examination at School*			
		No. who Completed the Skin test	*Percentages with Positive Tuberculin Reactions*		
			Positive to 3 TU	*Positive Only to 100 TU*	*Total Positive*
A	Children admitted concurrently with those given BCG vaccine — Negative unvaccinated	5,700	0·4	5·3	5·7
	Children admitted concurrently with those given BCG vaccine — Negative, BCG vaccinated	7,300	85·8	13·8	99·6
B	Children admitted concurrently with those given vole bacillus vaccine — Negative unvaccinated	2,600	0·0	5·2	5·2
	Children admitted concurrently with those given vole bacillus vaccine — Negative, BCG vaccinated	3,400	84·5	14·5	99·0
	Children admitted concurrently with those given vole bacillus vaccine — Negative, vole-bacillus vaccinated	3,600	59·8	34·6	94·4
	Period of vaccination				
C	Jan., 1951-July 1951 — Vole-bacillus vaccinated	1,700	29·4	58·8	88·2
	Sept., 1951-Dec., 1952 — Vole-bacillus vaccinated	1,900	87·5	12·5	100·0

Tuberculous Lesions attributed to Vaccination

In 5 participants tuberculous lesions which developed after vaccination were regarded by the assessor as complications of vaccination, to be classed with the complications referred to above. They were two cases of erythema nodosum occurring 1 month after BCG vaccination, and 1 case of cervical and 2 of axillary tuberculous adenitis which occurred 3, 6 and 8 months after vole-bacillus vaccination. In addition 22 cases were discovered showing lesions indistinguishable from lupus vulgaris, severe enough to require treatment, at the site of the puncture vaccination with vole-bacillus vaccine. These 22 cases all occurred among the participants (4,100) given the vaccine after it had been brought up to standard (see above). No such cases were discovered in the children vaccinated with BCG vaccine. All these 27 cases are excluded from Tables I and II. It is emphasized that there was no evidence that any of the other cases of tuberculosis in vaccinated participants were due to the vaccinating organism.

Incidence of Tuberculosis in the first 2½ years

By the end of June 1955 every participant had been in the trial for 2½ years, and the great majority of cases of tuberculosis starting within 2½ years of entry may be presumed to have come by now (January 1956) to the notice of the teams.

A total of 165 cases of definite tuberculosis started within the 30 months of entry to the trial (75 discovered by the teams radiologically and 90 discovered by the National Health Service), and a further 9 were assessed as possible tuberculosis. There were no deaths from tuberculosis. The number of cases in the 5 skin-test and vaccination groups are given in Table II*. Section A shows an annual incidence of 1·94 per 1,000 in the tuberculin-negative unvaccinated group, compared with 0·37 in the BCG-vaccinated group. (The possibility of this having occurred by chance is less than 1 in a million.) The annual incidence in the group initially positive to 3 TU was 1·75 per 1,000, compared with 0·74 in the group positive to 100 TU. The difference in incidence between the two positive groups, and also between the negative unvaccinated group and those positive only to 100 TU, is statistically significant ($0·01 > P > p·001$). The incidence in the BCG-vaccinated group is also substantially and significantly lower than that in the group initially positive to 3 TU ($0·001 < P$), but, while rather less, does not differ substantially from that in the group positive only to 100 TU ($0·2 > P > 0·1$).

Section B of Table II shows an annual incidence of 2·06 per 1,000 in the negative unvaccinated group, compared with 0·44 in the vole-bacillus-vaccinated group. (The possibility of this difference having occurred by chance is less than 1 in 10,000.) The difference between the annual rates for the vole-bacillus-vaccinated group (0·44) and for the concurrent group of BCG-vaccinated children (0·31) does not attain statistical significance.

If the 9 cases in which the assessor was in doubt over the diagnosis were included with the definite cases, the above comparisons would remain practically unaltered.

Of the 20 definite cases of tuberculosis in the vaccinated groups there was evidence in all except one (in a vole-bacillus-vaccinated participant, in whom no tuberculin test was made before the disease developed and no vaccination reaction was seen at the first re-examination, which was 2 years after vaccination) that the individuals had been satisfactorily vaccinated, as judged by the usual criteria. In one of the 20 (a BCG-vaccinated participant)—the only one known to have developed within 6 months of vaccination—it was considered that the disease might well have arisen before any protection had been conferred.

The Forms of Tuberculosis. In 104 of the 165 cases (63%) the form of tuberculosis that developed (or the major form) was pulmonary tuberculosis. There is no evidence of important differences between the 5 groups in the ratio of pulmonary to total cases (though the numbers of cases in the 2 vaccinated groups are small). Tuberculous meningitis (3) and miliary pulmonary tuberculosis (3) occurred in 6 of the 64 cases in the negative unvaccinated group. None occurred in any of the other groups.

Severity of Pulmonary Lesions. No important difference between the 5 groups was found in respect of extent of lesion or cavitation. Nor did a consideration of the treatment ordered by the physician responsible for the care of the patient reveal any important differences between the groups in regard to the severity of the lesions.

Other Particulars. Particulars are given in the report concerning the bacteriological and pathological investigations that were carried out, particulars bearing on the reliability of the independent assessments, and particulars concerning the starting point of the illness relative to the date of entry to the trial.

TABLE II. CASES OF TUBERCULOSIS STARTING WITHIN TWO AND A HALF YEARS OF ENTRY TO THE TRIAL

Section	Skin-test and Vaccination Group	Estimated No. of Participants	Definite Cases of Tuberculosis: No. Starting within 30 Months	Definite Cases of Tuberculosis: Annual Incidence per 1,000 Participants	Possible Cases of Tuberculosis Starting within 30 Months
A	Children admitted concurrently with those given BCG vaccine: Negative unvaccinated	13,200	64	1·94	2
	Negative, BCG vaccinated	14,100	13	0·37	2
	Positive to 3 TU	15,800	69	1·75	3
	Positive only to 100 TU	6,500	12	0·74	1
B	Children admitted concurrently with those given vole-bacillus vaccine: Negative unvaccinated	6,400	33	2·06	2
	Negative, BCG vaccinated	6,400	5	0·31	1
	Negative, vole-bacillus vaccinated	6,400	7	0·44	1
	Positive to 3 TU	8,600	37	1·72	2
	Positive only to 100 TU	3,500	6	0·69	0
C	All participants included in the above comparisons†	56,000	165	—	9

† That is, all participants in Section A plus the vole-bacillus-vaccinated group in Section B.

Supplementary Information on Cases of Tuberculosis starting after the first 2½ years. Some preliminary information is available on the continuance, beyond the first 2½ years, of the protection afforded by the vaccines. All the participants have now (January 1956) been in the trial for 3 years, some 4 years, and a few have completed 5 years. All cases of tuberculosis are being assessed as they come to the notice of the teams. Of the 75 cases that are known (up to date) to have started between 2½ and 4 years after entry, 38 are in the negative unvaccinated group, 5 in the negative BCG-vaccinated group, 0 in negative vole-bacillus vaccinated group, 24 in the positive to 3TU group and 8 in the positive only to 100 TU group. These figures afford no evidence of any diminution in the efficacy of either of the two types of vaccine up to 4 years.

DISCUSSION

The early results of the present trial provide clear evidence, for a period of 2½ years, of the efficacy of BCG vaccination, and also of

* Table IV in the original report.

vole-bacillus vaccination, in the prevention of tuberculosis in a group of adolescents living the ordinary urban and suburban life in an English industrial community with well-developed health services and with relatively low tuberculosis incidence and mortality.

The trial was confined to a narrow and susceptible age-group, viz. children nearly all between 14½ and 15 years, in the final year at 'secondary modern schools' at North London, Birmingham and Manchester, who volunteered with parental consent. The 56,700 participants came from a wide range of social and economic backgrounds and were initially free from active tuberculosis and from known contact with the disease at home.

All the participants are being kept under observation and when the trial was planned emphasis was laid on the need to detect and study cases of tuberculosis rather than deaths; in the event 165 participants are known to have developed tuberculosis within 2½ years of entering the trial, but there was no death from the disease during this period. A much longer period of observation will be necessary, but the early results are of sufficient importance to be considered and recorded. The scope of the report is also limited because the numbers of participants (though not the number of cases of tuberculosis) had to be estimated from representative samples of the records.

It is probable that few cases of tuberculosis have escaped detection, and there has been close correspondence between the diagnoses of the independent assessor, unaware of the vaccination history of the children, and those of the chest clinic and other physicians responsible for the investigation and treatment of the cases.

Protection afforded by Vaccination

In the first 2½ years the cases of tuberculosis that occurred in the tuberculin-negative unvaccinated group amounted to 1·94 per 1,000 per annum, as compared with a rate of 0·37 per 1,000 in the tuberculin-negative who received BCG vaccine (approximately one-fifth). Similarly the group of tuberculin-negative who received vole-bacillus vaccine gave an annual incidence of 0·44 per 1,000, or approximately one-fifth of the incidence of 2·06 per 1,000 amongst those admitted concurrently in the tuberculin-negative group. Thus the protective value of both vaccines was shown to be substantial. Both vaccines appeared to confer protection within 6 months, the protection was still substantial at 2½ years, and supplementary incomplete information suggests that the protection is maintained up to 4 years. (Aronson and Aronson—*J. Amer. Med. Assoc.* 1952, **58**, 255—reported that in North American Indians a substantial degree of protection from BCG vaccination was maintained for at least 10 years. The present report records the results of a few other trials of BCG vaccination in general population groups in other countries, in which tuberculin-negative subjects were selected by a random process either for vaccination or to be left unvaccinated).

The forms of tuberculosis and their severity were studied and have appeared to be similar in the vaccinated groups and the negative unvaccinated group. However the 3 cases of tuberculous meningitis and the 3 of miliary pulmonary tuberculosis were confined to the negative unvaccinated group.

Complications of Vaccination

With both vaccines occasional cases of regional adenitis and delayed healing of the vaccination lesion were recorded. In addition 2 cases of erythema nodosum developed after 4 weeks in the 14,100 participants given BCG vaccine. These complications have to be set against the efficacy of the vaccines in preventing tuberculosis. With the vole-bacillus vaccine the findings of earlier workers have been confirmed—that lesions indistinguishable from lupus vulgaris occasionally develop at the site of vaccination. These lesions have been severe enough to require treatment in 22 of the 6,400 participants given the vole-bacillus vaccine. This vaccine was given by multiple puncture and it is possible that the intracutaenous method will not produce this complication.

Incidence of Tuberculosis in those initially Tuberculin Positive

Considerable attention was given in this investigation to the behaviour in this report of the 22,300 participants who were tuberculin-positive on entry. Among those with a positive reaction to 3 TU on entry the annual incidence of tuberculosis (2½ years) was 1·75 per 1,000, as compared with 0·74 in those who on entry were negative to 3 TU but positive to 100 TU. Thus, as a group, those positive to 100 TU only were less likely to contract tuberculosis than those positive to 3 TU. Moreover the incidence of tuberculosis within the group positive to 3 TU was associated with the intensity of the initial reaction to tuberculin. For those with induration of 5-14 mm. to 3 TU the annual incidence was 0·78 per 1,000 (almost the same as for those initially positive only to 100 TU), but for those with larger reactions to TU the incidence was 2·93 per 1,000 (which is higher even than in the negative unvaccinated group).

These findings call for more investigation; it is hoped that further information from the present trial may become available in a later report.

Assessment of the Benefits of Vaccination

According to the present results, if *none* of the tuberculin-negative entrants had been vaccinated, 165 cases of tuberculosis would have been expected among them within 2½ years of entry; if *all* of them had received BCG vaccine, 30 cases would have been expected—a reduction of 82% in the expected incidence of *tuberculosis in the tuberculin-negative group*.

However, many of the children entering the trial were tuberculin-positive and thus not eligible for vaccination. They produced 81 cases of tuberculosis in 2½ years; including these the expected reduction in the total number of cases in 2½ years if all the tuberculin-negative entrants had been vaccinated would have been from 246 (165+81) to 111 (30+81)—a reduction of 55% in the incidence of tuberculosis in the tuberculin-negative and tuberculin-positive groups combined.

This estimate, however, has been calculated after the exclusion of 134 previously unsuspected cases of definite tuberculosis which were present on entry to the trial (nearly all detected from the initial radio-graphic examination at school). If the preliminary X-ray had not been taken many of the 134 cases would apparently have arisen *after* entry and would have increased the total cases amongst those initially tuberculin-positive from 81 to a figure of the order of 200. The apparent reduction in the total number of cases within the 2½ years, as a result of giving BCG to all those initially tuberculin negative, would, in the absence of an initial radiograph, have been of the order of 35% (from 165+200 to 30+200). As a corollary, in any scheme of vaccination in adolescence, X-ray examination and follow-up of those found at the outset to be tuberculin-positive, particularly those with strong reaction, should be considered.

The benefit to be expected from BCG vaccination may also be experienced in terms of the administrative action required. The expected reduction of 135 cases in the first 2½ years would have resulted from the tuberculin-testing of 56,000 school-children and the BCG vaccination of the 33,700 negative reactors. This corresponds to the prevention of 1·6 cases annually (for 2½ years) among every 1,000 children given BCG vaccine, or the prevention of 1·0 cases of tuberculosis annually (for 2½ years) for every 1,000 children given tuberculin tests preparatory to vaccination. The expected results if vole-bacillus vaccine were used in place of BCG would be very similar.

It is to be borne in mind that the participants were vaccinated towards the end of their 15th year, by which time 40% were tuberculin-positive. The experience of this trial indicates that it might be desirable to vaccinate school-children at an early age, before so large a proportion of them had been infected naturally. However, not until further information becomes available on the duration of the protection afforded by vaccination, and this is considered in relation to the proportion of children who are tuberculin-positive at different ages, will it be possible to judge the optimum age at which to institute a scheme for a single vaccination of adolescents.

Finally it should be borne in mind that the cases discovered in the group tuberculin-negative on entry and remaining unvaccinated are manifestations of tuberculosis appearing within a few years of natural first infection, and that the protection shown to have been afforded by vaccines concerns these manifestations. The investigation provides no information about the development of tuberculosis in the vaccinated participants during later life.

The trial is still in progress, and later reports will contain detailed analyses over longer periods of time.