The Effectiveness of B.C.G. Vaccination in Africans

BY

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A good trial of B.C.G. vaccination compares results in the vaccinated group with those in a tuberculin-negative control group. Frequently in underdeveloped countries, however, the prime object is to vaccinate as many as possible to combat a high and increasing disease rate, and there is neither time nor staff to plan and carry out a properly-controlled trial. The present study attempts to overcome this difficulty to some extent by a careful use of statistical methods and ends, it is believed, with a reasonably reliable proportion for those protected.

The second essential quality of a good trial of B.C.G. vaccination is that it seeks the proof of the pudding in the eating. It should preferably not be done, for instance, by observing the length of time before tuberculin reversion occurs after vaccination, nor even by finding the numbers in vaccinated and unvaccinated groups who show radiological evidence of tuberculosis after a given interval. The ideal is to be able to compare, in the two groups, the numbers that fall ill with the disease. In this study it has not been possible to do this *in toto*, but samples have been obtained by using all those reporting to hospital with tuberculosis.

No previous study of the value of B.C.G. in Africans appears to have been published. The most useful, most comprehensive and best-controlled experiments carried out in other parts are listed below, together with the results obtained.

In addition, the spontaneously-occurring experiment described by Hyge (1956) deserves mention. In this case, where 94 tuberculin-negative unvaccinated children and 106 vaccinated children were exposed to a tuberculous teacher, 41 and two children respectively developed progressive tuberculosis—a protection rate of 96 per cent.

Material

The study was associated with a B.C.G. vaccination campaign which covered all the African schools in the eastern province of Southern Rhodesia once, and lasted from January, 1955, to June, 1958. All these children had been tuberculin-tested by the author. Approximately 50,000 children were involved, about 45,000 receiving the Mantoux test with 5 T.U. of Old Tuberculin, while the other 5,000 were given the Heaf multiple-puncture test using a dilution of 1/15 Old Tuberculin, which had been shown to be approximately equivalent to the Mantoux 5 T.U. (Shennan, 1961). All negative reactors were given Danish B.C.G., which was full strength (0.75 mg./mil.), from January, 1955, to April, 1956, and was then supplied as half strength (0.375 mg./mil.) until the end of the period. The dose was 0.1 mil., given by intradermal injection.

Method

All children aged 6-18 notified as tuberculosis cases from hospitals in the eastern province—also called Manicaland—during the period April, 1956, to April, 1959, were followed up to discover whether they had been at school and, if so, whether the records showed that they had been tuberculin-tested at school and/or given B.C.G. Those who had been tested but were absent at the second visit were counted as having not been tested.

The number of children who could have entered the province after being tested elsewhere was negligible. No previous work of this kind had been done in Manicaland, so that any child reported as having been tested or given B.C.G. would have been done in the course of this campaign.

An estimate was made of the average number of children at school in the province from January, 1956, to December, 1958. This could be done fairly accurately with the help of figures obtained from the African Education Department.

The average number of *tested* children was then calculated on the basis of the numbers who had been tested at the beginning and end of each year, together with the proportions of all school children leaving at the end of each year.

The numbers at risk were based on the numbers at school and those tested from January, 1956, to January, 1959, i.e., three months earlier than the period of observation. The interval

Author	Details of Work	Protection Rate. Per Cent.
Dahlstrom and Difs, 1951.	Swedish soldiers, 36,235 vaccinated, 25,239 negative controls.	77
Gernez-Rieux *et al.*, 1955.	School children aged 6-14, by scarification, 15,284 vaccinated, 2,130 negative controls.	90
Medical Research Council, 1956.	School children aged 14½-15, Danish full-strength vaccine, 14,100 vaccinated, 13,200 negative controls.	81
Aronson *et al.*, 1958.	North American Indians, follow-up after 18-20 years, 1,547 vaccinated, 1,448 negative controls.	82

was decided quite arbitrarily and was intended to make some allowance for the time between onset of disease and coming to hospital.

The method outlined above was adhered to regardless of any apparent errors resulting, as it seemed that the most reliable results would be obtained by such rigidity. For instance, of the five children who were found to have developed tuberculosis after having had B.C.G., one case occurred within one month of the vaccination so could not possibly have been protected by it. Exclusion of that case, however, would have meant that an unknown number of cases in the positive-reacting group, which also began prior to the time of testing, would have to be left out; and a corresponding number of untested children, even more impossible to calculate, would require similar treatment.

The analysis has two stages. Firstly, it compares directly the proportion of school children coming to hospital with tuberculosis who had been tested and given B.C.G. if negative with that of children who had not been tested. From these the percentage protection afforded by the whole operation of tuberculin-testing and B.C.G. vaccination can be worked out. The second stage divides the tested group into those who had been positive reactors and those who had been negative and were given B.C.G. It aims to find out the proportion of negative reactors who are protected by the vaccine and gives a better idea of its specific value. This method, of course, is used in all controlled trials of B.C.G. The basis of the analysis used here was to create a *theoretical* control group by assuming that the proportion of positive reactors coming to hospital from the untested group would, if they had been tested at school, be the same as in the tested group. Hence the rest of the untested group would have been negative reactors; this number of negative reactors then forms the control for comparison with those who had received B.C.G. The standard error of the proportion protected thus obtained can be calculated.

Difficulties and Inaccuracies

Where it was impossible to avoid a source of error the tendency was to make the error adverse to B.C.G. rather than the other way, so that it would be possible at the end to say that *not less than* so many per cent. were protected by the vaccine.

Difficulty in Identifying the Patient

Although in general the hospital staffs were very helpful in putting the required details on the notifications, it often happened that the age of a child was not given, so that one did not know if he was of school age, or that the school was not stated. This meant long and tedious correspondence, as most cases were in country hospitals, and it was inevitable that sometimes the information would be lost.

Another embarrassment was the tendency for the children to use different first names; this may be alternating from tribal to Christian name, or on occasion the result of being converted from one Christian religion to another. Further confusion was caused by the multiplicity of family names, *mutupo*, *chidawo* and possibly others, which appear to be interchangeable.

Towards the end of the study the possibility of a child having moved from one school to another increased, meaning that some children stating that they were at one school would not be found in the index, but would nevertheless have been tested at another school.

All cases of doubt were treated separately, as shown below.

Variations in Accessibility of the Different Areas

Testing was done at all schools, but some areas were much more remote from hospitals than others. This would create bias in that the remote areas would detract from the number of hospital patients in the group in which they predominated (tested or untested). If the remote areas were tested first they would contribute more child-years to the tested group, causing an unfair swing in its favour (i.e., fewer cases of tuberculosis found in the tested group). In fact, however, the tendency was to test the more accessible areas first, so that here the bias will swing, if at all, against the tested group.

RESULTS

Two groups of figures have to be found. These are: two denominators (the average numbers of tested and of untested children at school during the years under study) and three numerators (the number of B.C.G.'d negative reactors, of positive reactors and of untested school children notified from hospital as tuberculosis cases during the same period).

A. *The Denominators*

Lines (1), (2) and (3) of Table I are figures made available by courtesy of the African Education Department in Umtali. The average school population over the period is easily calculated (line (2)).

The average number of children *tested* over the whole period is obtained by working down each year column from line (4) to line (8) and by calculating line (8) from lines (2), (3) and (6). Line (4) for the next column is then derived from lines (6) and (8) of the original column. The table shows that on the average, working to the nearest thousand, 28,000 children were in a tested state during the three years.

The average number of untested children is then 61,000—28,000=33,000.

B. *The Numerators*

During the observation period 143 children of school age (6-18) were notified from hospitals as suffering from tuberculosis. Sixty-nine of these were known to have been at school in the eastern province and their distribution was as follows:

Tested at school, negative reactor, given B.C.G.	5
Tested at school, positive reactor	13
Definitely not tested at school	39
Probably not tested at school, B.C.G. state unknown	6
Probably not tested at school, no B.C.G. mark	6

The age distribution between the groups was very even, as shown in Table II. The table also gives the sex distribution, and it will be seen that all the cases occurring after B.C.G. vaccination were girls; of those who had been positive at school there were twice as many boys as girls, and the untested group contained twice as many girls as boys. In the whole tested population there was a slight predominance of boys.

(1) *Number of Untested School Children Notified by Hospitals as Tuberculosis Cases*

This figure, as will be seen from the numbers quoted above, was the most difficult of the five

Table I

DERIVATION OF AVERAGE NUMBERS OF TESTED AND UNTESTED CHILDREN AT SCHOOL IN THE YEARS 1956 TO 1958 INCLUSIVE

	1955	1956	1957	1958 Jan.-June, 1958 (5 months)	1958 June, '58-Jan., '59 (7 months)	Total School Years, 1956-58	Average
(1) Newcomers in Jan.	—	13,000	15,000	15,000			
(2) Enrolment	54,000	57,000	61,000	65,000		183,000	61,000
(3) Leavers in Dec.	10,000	10,000	11,000	12,000			
(4) Tested pop. at start of year	—	9,780	22,080	31,210	36,210		
(5) Tested during year	12,000	17,000	16,000	5,000	—		
(6) Tested pop. at end of year	12,000	26,780	38,080	36,210	36,210		
(7) Average tested pop.	N/A	18,280	30,080	33,710	36,210		
				35,168		83,528	27,843
(8) No. tested children leaving at end of year	2,220	4,700	6,870	—			

Table II

Age and Sex Distribution of School-Age Tuberculosis Cases

	Boys	Girls	Mean Age
Negative, given B.C.G. at school	—	5	12.2
Positive reactors at school	9	4	12.1
Not tested at school	17	34	12.1
All cases	26	43	12.1

to determine. There were 51 children notified for whom no records were found in the cards of the school which they had been attending. In six cases it was not possible to determine definitely that they were not tested, nor was it discovered whether they had B.C.G. marks. It was considered "safe" to say that two of these were in fact not tested and to exclude the other four on the grounds that they might have been tested, i.e., it was thought that this procedure, though it might give too low a result for the proportion protected, could not result in one which was too high. Thus 47 of these 51 children were included in the analysis.

Of these 47, there were six who had no B.C.G. mark, but could not be said definitely not to have been tested and found Mantoux-positive. In the same period as these 47 there were 13 cases who had been Mantoux-positive when tested at school; hence the proportion of the six who might be expected by chance to have been Mantoux-positive, even had no efforts such as questioning been made to exclude these, would be $\frac{13}{41+13} \times 6$, or just under $1\frac{1}{2}$ children. It is therefore "safe" to assume that two of the 47 were in fact positive reactors, giving 45 in the untested group. The chances of there being more than two positive reactors out of the six are one in six, but to this must be added the fact that all the six children were asked whether they had been tested and stated that they had not.

(2) *Number of Cases Who Had Been Found Positive on Testing at School*

The number found was 13; but in order to be "safe," as indicated in (1) above, two more must be added to make it 15.

(3) *Number of Notified Cases Who Had Been Tested at School and Received B.C.G.*

This was five.

The figures used for the final analysis are therefore as summarised in Table III.

Table III

Corrected Figures Used for Assessment of the Value of B.C.G.

Tested population at risk of coming to hospital with tuberculosis	28,000
Untested population at risk of coming to hospital with tuberculosis	33,000
Hospital cases who had been tested, negative, given B.C.G.	5
Hospital cases who had reacted positive when tested	15
Hospital cases who had not been tested at school	45

Protection Conferred on Children by the Whole Process of Tuberculin Testing and Giving B.C.G. to the Negative Reactors

Of 28,000 children tested at school, 20 appeared in hospital with tuberculosis.

Of 33,000 children not tested at school, 45 appeared in hospital with tuberculosis.

Out of 28,000 children, this latter number would have been $\frac{45 \times 28{,}000}{33{,}000} = 38.15$ children.

The proportion protected is therefore

$$\frac{38.15-20}{38.15} \times 100\% = 47\%$$

Protection Conferred by B.C.G. Vaccine on Negative Reactors

Number of positive reactors occurring in the tested group was 15.

Number of positive reactors expected in the untested group, therefore, is $\frac{15 \times 33{,}000}{28{,}000} =$ 17.70. Hence number of negatives expected in untested group is $45-17.70=27.30$. Thus number of negatives expected in tested group $= 27.30 \times \frac{28{,}000}{33{,}000} = 23.15$.

Observed number of negatives (given B.C.G.) in tested group was five, hence protection rate was $\frac{23.15-5}{23.15} \times 100\% = 78\%$.

Probability Limits

These are regarded as being the highest and lowest real values for the protection conferred by B.C.G. for which, if repeated trials like this were done, a figure as low, or as high, as our 78 per cent. would occur once in 20 trials.

It can be shown that where five out of 23 individuals in a group have a characteristic, 96 per cent. of chance readings will be within the range two to nine out of 23, 2.3 per cent. below and the rest above. Thus the upper likely limit of protection is $\frac{23-2}{23} \times 100\%$ or 91%, and the lower limit is $\frac{23-9}{23} \times 100\%$ or 61%.

The protection conferred by B.C.G. vaccine was therefore 78 per cent., with probability limits from 61 to 91 per cent. Since care was taken throughout to err against the vaccine rather than in its favour, this could be reworded to say that the protection was not less than 61 per cent.

Description of the Five Cases of Tuberculosis Occurring in Those Who Had Had B.C.G. Vaccine
(These were all girls)

(1) *Violet, Aged Nine*

Was a negative reactor to a test given on 6th February, 1956, and was given B.C.G. on the 9th. She was notified as a case of tuberculosis on the 27th July, 1956, when a B.C.G. scar was seen on the shoulder. She was found to have a history compatible with pulmonary tuberculosis, a positive Mantoux test, a positive sputum for M tuberculosis, and on X-ray enlarged hilar glands with a slight right apical shadow. She was discharged from hospital in August, 1956. She was found at school by the health inspector in November, 1956, when she was well. In December, 1957, she was re-examined by the doctor who notified her and was found to be gaining weight and to have no cough. X-ray showed the hilar glands to be still present, but smaller.

(2) *Magrose, Aged Twelve*

Was a negative reactor to a Mantoux test given at school on the 24th September, 1956, and was given B.C.G. on the 27th September. She was admitted to hospital in May, 1957, with a history of about two months' illness. She had a B.C.G. scar on the shoulder and gave a well-marked positive reaction to the Mantoux test. X-ray showed an Assman's focus. Treatment began on the 24th May, 1957. She must have been discharged some time before October, since during that month she returned for review. The author visited her at home in December, 1957, when she looked very well and was symptom-free.

(3) *Josephina, Aged Nine*

Reacted negative to a Mantoux test given on the 31st March, 1958, and received B.C.G. on the 3rd April, 1958. The onset of symptoms was within a month after B.C.G. was given, so that the vaccine could not have had any effect before the disease was established.

(4) *Christina, Aged Thirteen*

Was Mantoux-tested on the 28th October, 1957, and, reacting negative, was given B.C.G. on the 31st October. She was admitted to hospital with "several months'" history of illness shortly before her transfer to another hospital on the 22nd August, 1958. She was notified as a case of tuberculosis on the 21st October, 1958. It was not established that she had a B.C.G. mark, but her identity was proved by referring back from the B.C.G. record card to the school. She died on the 30th December, 1958, after an illness with bizarre clinical features. At the first hospital where, at the time, no doctor was available she had been treated with penicillin, which did not bring about any improvement. She had then been seen by the doctor and transferred to the larger hospital as a cardiac case. X-ray then showed "a huge mitralised heart, enlarged hila (right more than left) and infiltration into both lungs." Blood sedimentation rate was 130 mm. in one hour (Westergren). The Mantoux test 1/1,000 was strongly positive. The temperature was very high, but settled to normal within a few days on streptomycin. Streptomycin was abandoned in December on the grounds that the hearing became affected. The other antituberculous drugs were not given because of poor tolerance.

By the end of October there was considerable improvement in both pulmonary and heart conditions radiologically and in her general state. The heart was almost of normal shape, the hila were nearly normal and there was only a little infiltration of the lung parenchyma. On 16th December, however, she collapsed suddenly and from then on went downhill until her death on the 30th.

On the evidence available there seems little doubt that she had tuberculosis and that this was of the primary type and fairly severe. At the same time it seems that it did not cause her death, particularly as she had responded well to about three months' treatment with streptomycin before her sudden decline began.

(5) *Betty, Aged Sixteen*

After receiving the Mantoux test on 12th April, 1955, and reacting negatively, she was given B.C.G. on the 15th. She was admitted to hospital in February, 1959, with a two months' history of illness and was notified as a case of tuberculosis on 7th March. The "probable date of infection" was given as June, 1958.

The author visited her in hospital on 21st April, 1959. The doctor being away at the time, the original X-ray was not available, but it happened that a new film was taken that day and this showed infiltration in the left lung. No positive sputum had been obtained. On examination, she was seen to be dyspnoeic. She had had 54 days' treatment with streptomycin and I.N.H. There was a B.C.G. scar on the left shoulder.

It is evident, then, that she was a moderately severe case of pulmonary tuberculosis.

To sum up, the five children who developed clinical tuberculosis after having had B.C.G. vaccine can be classified as follows:

(a) One case which developed before the B.C.G. vaccine could take effect.

(b) Two minimal cases, one with features of primary and the other of secondary disease; onset about five and about six months after vaccination.

(c) Two moderately severe cases, both with primary features; symptoms began, in one case, something under nine months after vaccination, and in the other the period was three years and eight months.

CONCLUSIONS

In the Bantu, as judged by school-age children in Manicaland, B.C.G. vaccination appears to be about as effective as in the various other races and nations studied. Cases of failure do occur and can result in serious tuberculous disease.

Although the controlled trial is, as ever, the ideal method of testing a vaccine, it is possible to obtain useful results in the course of a straightforward vaccination campaign and in the face of very limited vital statistics. The method involves the use of the as yet unvaccinated element of the population, the careful consideration of all possible sources of error, and the elimination of these either by working out the probable error involved at each stage or by taking the figure least favourable to the vaccine that is under trial.

SUMMARY

An analysis was made of school children notified as cases of tuberculosis, dividing them into those who had and those who had not been tuberculin-tested and/or given B.C.G. vaccine at school in the course of a B.C.G. vaccination programme. By using a calculated theoretical "control group" it was found that B.C.G. is about 78 per cent. effective in African school children, with probability limits from 61 per cent. to 91 per cent.

Case details are given of the five children who developed tuberculosis after having been given B.C.G. vaccine.

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