Evaluation OF BCG Vaccination among Puerto Rican Children

GEORGE W. COMSTOCK
VERNA T. LIVESAY
SHIRLEY F. WOOLPERT

A follow-up study of large scale tuberculin testing and vaccinating in Puerto Rico reveals that BCG vaccination had little overall effect in reducing the incidence of tuberculosis and did not reduce the severity of cases occurring among nonreactors.

Introduction

In 1946, the Surgeon General of the U.S. Public Health Service appointed the first of a series of advisory committees to consider the potential role of BCG vaccination in this country. After reviewing the evidence available at that time, the committee made a number of recommendations.[1] Among them was that the usefulness of BCG vaccination be evaluated in several different populations. The first response to this charge was a controlled trial among school children in Muscogee County, Georgia.[2,3] As a contrast to that community with a tuberculosis problem that seemed about average for the United States, Puerto Rico was selected for a further large scale trial.

The authors are with the Research Section, Tuberculosis Program, Center for Disease Control, Public Health Service, U.S. Department of Health, Education, and Welfare, Bethesda, Maryland, and the Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland. The preparation of this report was supported in part by Research Career Award HE 21,670 from the National Heart and Lung Institute, Public Health Service, U.S. Department of Health, Education, and Welfare. Requests for reprints should be addressed to Dr. G. W. Comstock, Training Center for Public Health Research, Box 2067, Hagerstown, Maryland 21740. This paper was presented before the Epidemiology Section of the 100th Annual Meeting of the American Public Health Association, November 13, 1972.

The tuberculosis death rate in Puerto Rico had risen throughout the first third of the present century, reaching a peak of over 300 deaths per 100,000 in 1933.[4] Thereafter, it fell at a fairly constant rate to just below 200 per 100,000 in 1948. As in nearly all countries, the decline then accelerated rapidly for a while, so that the mortality rate in 1953 was below 50. The rate of decline then began to slow down. By 1969, the annual tuberculosis death rate had only dropped to 12 per 100,000.[5]

Throughout this entire period, mortality rates indicated that the tuberculosis problem in Puerto Rico was among the world's most serious. The situation at midcentury was clearly such that most of the world's tuberculosis experts would have unhesitatingly recommended that BCG vaccination be added to the tuberculosis control program. Furthermore, most of them would have expected it to have a major impact on the problem. Tuberculosis was thought to arise mainly from recently infected persons, who could be protected if they were vaccinated prior to exposure. Healthy tuberculin reactors, having passed unscathed through this initial period of high risk were then believed to contribute relatively little to the tuberculosis problem.

The vaccination trials conducted by the U.S. Public Health Service, including the one in Puerto Rico, were designed to test both of these assumptions, specifically that most tuberculosis would arise from recently infected persons and that BCG vaccination would materially decrease their risk of developing manifest disease. The

validity of these two assumptions would obviously determine the usefulness of BCG vaccination as a public health measure.

Materials and Methods

Most of the procedures of this trial have been described previously.[6] The program was sponsored by the Puerto Rico Departments of Health and Education and the U.S. Public Health Service. It was deliberately designed to resemble as closely as possible the mass BCG vaccination campaigns being conducted at that time in many parts of the world. Like these campaigns, it would be limited to children.

Tuberculin testing and vaccinating were started in September, 1949, and stopped in May, 1951. Most of the schools in Puerto Rico were visited during this period. Children not in school were invited to the school programs and also to special clinics set up in the summer of 1950. Owing largely to adverse publicity emanating from political opponents of the incumbent government, participation was much less than anticipated. Approximately 45 per cent of the school children took part; very few of the children not in school participated.

The program started in the poorer parts of the cities. Because tuberculin sensitivity was presumed to be very high in these areas, the initial screening dose of tuberculin was only 1 Tuberculin Unit (TU) of purified tuberculin. Children with less than 6 mm of induration to this screening dose were tested with 10 TU. Later in the program, the use of the 1 TU dose was discontinued, as it became apparent that there were very few severe reactions to an initial dose of 10 TU. All children with less than 6 mm of induration to 10 TU were considered eligible for vaccination. However, some of the eligible group did not wish to be vaccinated, largely because of the unfavorable publicity; they are classed as refusals. The remaining eligibles were divided into two groups on the basis of their birth years. As a concession to those who strongly favored BCG vaccination, the vaccinated group was to be twice as large as the control group. For each group of 3 consecutive birth years, children born in the central year were allocated to the control group. Those born in the other 2 years were allocated to the vaccinated group (vaccinees). Both controls and vaccinees received a test with 100 TU of tuberculin which served as a sort of placebo, in that both groups received an injection which often caused a reaction. Vaccinees were also given BCG at this time. The small numbers of children who erroneously received or did not receive BCG vaccine, or who had medical contraindications to vaccination, have been excluded from this analysis, as have the small numbers of children below 1 and above 19 years of age.

All tests and vaccinations were performed by specially trained nurses. The tuberculin was RT 19-20-21 supplied by the Statens Seruminstitut in Copenhagen, Denmark. The transverse diameter of any resulting induration was carefully measured on the 3rd day after testing. BCG vaccine, supplied by Dr. K. Birkhaug from the New York State Department of Health, Albany, New York, was shipped by air in refrigerated containers and used on the 3rd or 5th day after preparation. It was protected against both light and heat. A dose of 0.1 mg of BCG organisms in 0.1 ml of diluent was given intracutaneously over the insertion of the left deltoid muscle.

Much attention was given to ensuring that all study groups were treated similarly after the initial procedures. Publicity for the trial was done as if it were a one-time affair to avoid attracting attention to the fact that information on tuberculin and vaccination status would be kept for subsequent follow-up. All studies of postvaccinal sensitivity were based on the results of tuberculin testing among general populations, again to ensure that no study group would be singled out for special attention. Deaths and tuberculosis cases have been identified through routine notifications to official agencies. These records have been carefully matched against the study files by following specific written rules and without regard to the study category of the subjects.

Records of deaths and cases from Puerto Rican sources have been collected from the start of the trial through June 30, 1969. Because follow-up studies showed that half of the emigrants from Puerto Rico went to New York City, records of persons listed in New York City tuberculosis registers who had been born in Puerto Rico in the appropriate years were also matched against the study files in 1966. This effort yielded 104 additional cases. This search has not been repeated because of financial limitations. Potential follow-up for study participants ranges from 18.1 to 19.8 years; the average period is 18.8 years.

Results

Initial Tuberculin Sensitivity

A total of 191,827 children are included in the study population. Their distribution by age, study group, and tuberculin sensitivity on entry into the trial is shown in Table 1. Except where specifically stated otherwise, reactors are persons with induration measuring 6 mm or more in diameter to either 1 or 10 TU. The reactors can be divided into two groups: (1) screened reactors, who had the 1 TU dose administered first and who were given the 10 TU dose only if they had less than 6 mm of induration to the 1 TU dose; and (2) direct reactors, who were tested initially with the 10 TU dose.

The frequency of children with reactions measuring 6 mm or more in diameter to 1 or 10 TU of RT increased in almost linear fashion with age, attaining a level of nearly 75 per cent by age 18 for urban residents, and 62 per cent for rural residents. This is shown in Figure 1. Both curves tend to be slightly concave upward, a configuration that is consistent with a declining risk of infection during the lifetime of these children. Nevertheless, frequencies of reactors in the 2nd year of life of 7 per cent among urban children and 5 per cent among rural children suggest a

TABLE 1—Percentage Composition of Study Population and Major Age Groups by Study Category and Initial Tuberculin Sensitivity

Study Category	Size of Reaction to Specified Dose of Tuberculin	Age Group			
		Total	1–6	7–12	13–18
Total number		191,827	25,103	95,114	71,610
Total %		100.0	100.0	100.0	100.0
Screened reactors	1 TU				
	16+ mm	3.6	0.2	3.2	5.3
	11–15 mm	6.3	0.3	5.8	9.2
	6–10 mm	12.8	0.5	11.2	19.2
Screened reactors	10 TU				
	10+ mm	1.4	0.1	1.4	2.0
	11–15 mm	3.2	0.1	2.6	4.8
	6–10 mm	7.8	0.7	7.1	11.2
Direct reactors	10 TU				
	16+ mm	3.9	7.2	3.2	3.6
	11–15 mm	1.7	2.5	1.3	1.8
	6–10 mm	2.3	4.0	1.9	2.2
Refusals	10 TU				
Control birth years	0–5 mm	5.1	2.0	7.0	3.8
Vaccinee birth years	0–5 mm	11.3	6.6	14.3	9.0
Controls	100 TU				
	6+ mm	3.9	2.6	4.2	4.0
	1–5 mm	2.8	3.5	3.0	2.2
	0 mm	5.8	14.5	6.0	2.6
	No reading	1.7	3.2	1.8	1.2
Vaccinees	100 TU				
	6+ mm	6.7	5.9	6.9	6.7
	1–5 mm	5.1	7.3	5.4	4.0
	0 mm	11.5	31.3	10.8	5.4
	No reading	3.1	7.6	2.9	1.8

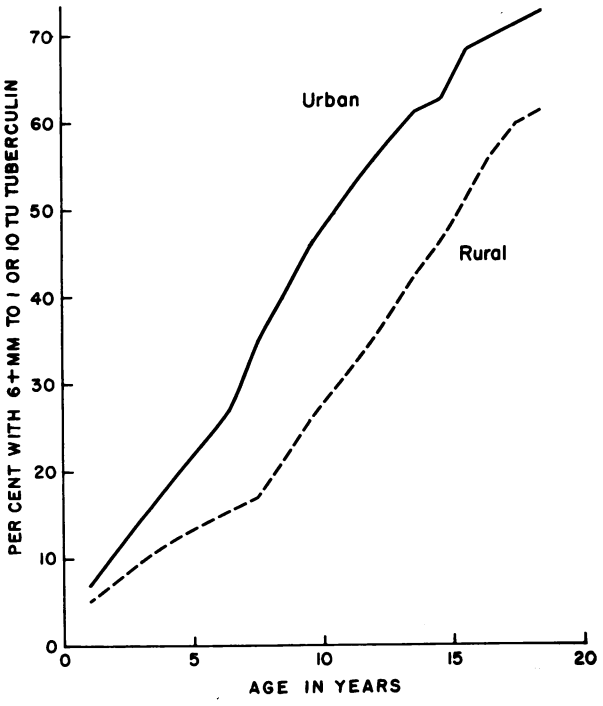

figure 1 Frequency of reactors to 1 TU or 10 TU of tuberculin, by age and place of residence.

recent and serious tuberculosis problem. Not many areas of the world now have higher infection risks than this.

A sizable proportion of nonreactors to 10 TU of RT reacted to the 100 TU dose. This is shown in Figure 2. The proportion of reactors to the 100 TU dose was higher among rural than urban residents at nearly all ages, reaching a level of approximately 50 per cent after the age of 15 years.

Postvaccinal Tuberculin Sensitivity

A sample of 259 controls and 555 vaccinees was included in a tuberculin testing program conducted approximately 5 years after the midpoint of the testing and vaccination phase of the trial. Their distributions according to size of reaction to 10 TU of RT were markedly different, as shown in Figure 3. Forty-one per cent of the controls and only 6 per cent of the vaccinees had no measurable induration, while 93 per cent of the vaccinees and 43 per cent of the controls had reactions 6 mm or more in diameter. An indication of the high degree of allergenicity of this vaccine is afforded by the distribution of reaction sizes among vaccinees, which is essentially the same as that observed among persons infected with *Mycobacterium tuberculosis.*[7]

As a possible further check on the long term

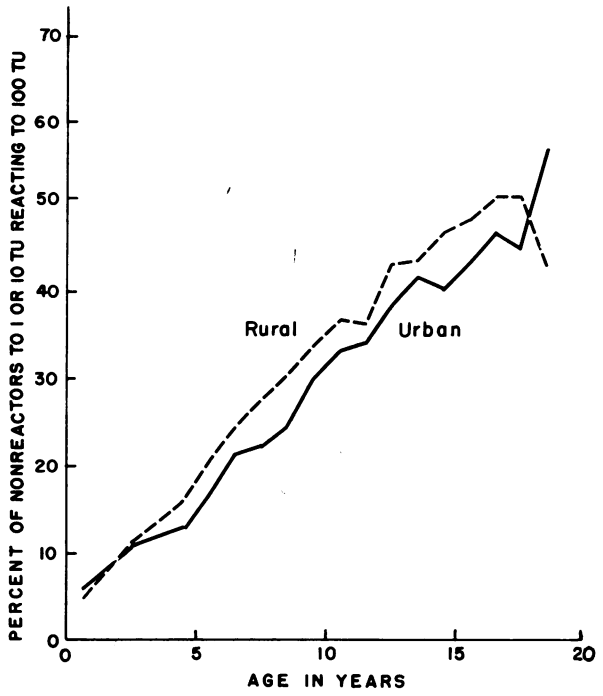

figure 2 Frequency of reactors to 100 TU of tuberculin among nonreactors to 10 TU, by age and place of residence.

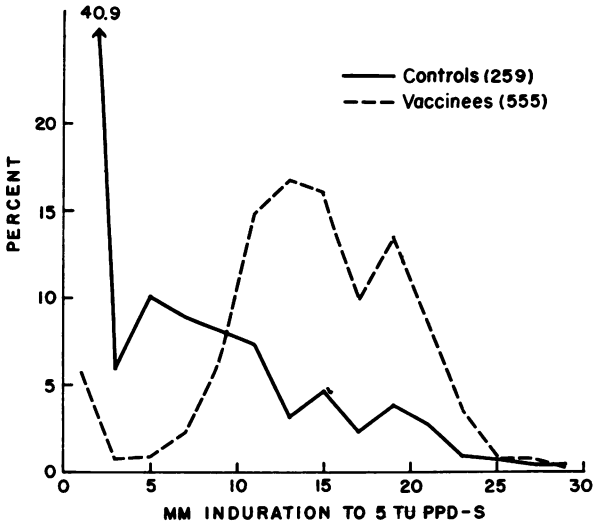

figure 3 Frequency distribution of controls and vaccinees by size of reaction to 10 TU of tuberculin 4 to 5 years after vaccination.

persistence of postvaccinal sensitivity, the records of Navy recruits tested between 1958 and 1965 were searched for participants in this trial. Unfortunately, Puerto Ricans do not have a tradition of enlisting in the Navy. Only 11 participants could be identified. Of these, four classified as reactors in the trial all had reactions of 10 mm or more to 5 TU of PPD-S on entrance into the Navy, with a mean reaction size of 13.2 mm. Three controls were located. One had a reaction of 8 mm of 5 TU of PPD-S and the other two had no measurable reactions to PPD-S or to two other

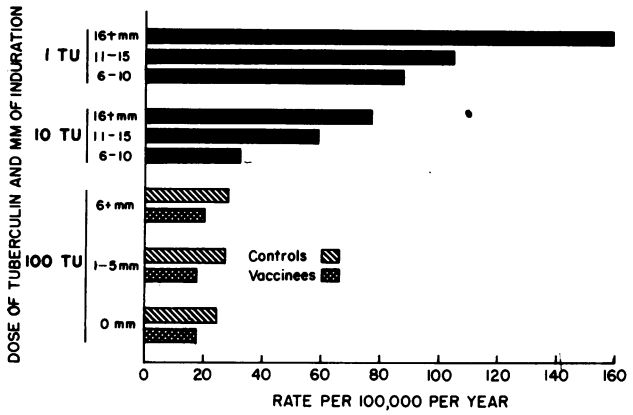

figure 4 Incidence of tuberculosis by initial tuberculin sensitivity and vaccination status.

mycobacterial antigens. Of the four vaccinees who entered the Navy during this period, all had some induration to 5 TU of PPD-S, with a mean reaction size of 11.8 mm at that time.

Public Health Usefulness of Vaccination

For the major thrust of this paper, the results will be presented in the form of answers to three questions, the same three asked and answered earlier on the basis of 7 years' experience.[6] These questions stress the oft-neglected public health usefulness of vaccination, which depends not only on the effectiveness of vaccination in preventing tuberculosis among nonreactors but also on the proportion of subsequent cases that would be destined to arise among them without vaccination. If most tuberculosis were to come from persons who are already infected, the role of vaccination would be limited regardless of its effectiveness. On the other hand, a vaccine of even modest effectiveness could have an important impact upon a tuberculosis problem arising largely among persons who had not yet been infected at the time of vaccination.

The three questions are as follows:

1. What proportion of the total number of cases of tuberculosis in the study population could have been prevented by a completely effective vaccination? In other words, what proportion of cases would have come from the group of initial nonreactors to tuberculin if no vaccinating had been done?
2. How effective was vaccination among persons who were vaccinated?
3. What proportion of the total number of potential tuberculosis cases could have been prevented by vaccinating all nonreactors?

To answer the first question, it is necessary to estimate the number of tuberculosis cases that would have occurred among nonreactors if none of them had been vaccinated. The expected number of cases among vaccinees is obtained by multiplying the number of vaccinated persons by the case rate among controls. This expected number is then added to the observed numbers of cases among controls and

among refusals, yielding an estimate of 576 cases among nonreactors without vaccination, shown in Table 2. Among the total 1,976 cases expected without vaccination, 29 per cent would have occurred among nonreactors. This proportion changed appreciably over the 20-year interval, being approximately 25 per cent for the first 10 years and 40 per cent for the second decade (Table 3). The proportion of cases arising among nonreactors without vaccination also varied with the age of the subjects. Among those who were 1 to 6 years of age initially, 48 per cent of the potential tuberculosis problem arose among nonreactors, contrasted with only 20 per cent among subjects aged 13 to 18 initially.

The answer to the second question is obtained by a simple comparison of the incidence rates among controls and vaccinees. This information is shown in Table 4. The average annual tuberculosis case rates among controls was 27.6 per 100,000 and among vaccinees was 19.7 per 100,000, a reduction of 28.7 per cent. The 95 per cent confidence limits around this percentage reduction are 44.7 and 12.9 per cent.

Tuberculosis case rates among controls and vaccinees are shown for various demographic subgroups in Table 5. The reduction in tuberculosis attributable to vaccination showed only minor variations by age and race. The effectiveness of BCG was significantly greater among males than among females. Although the effectiveness was also greater among urban residents than among country dwellers, this difference was not statistically significant.

The number of cases among both controls and vaccinees tended to diminish with the passage of time, as summarized in Table 6. The reduction in tuberculosis among nonreactors attributable to vaccination showed considerable fluctuation in successive 5-year periods, but none of the values for individual 5-year periods differed significantly from the overall reduction of 28.7 per cent.

The potential public health usefulness of BCG vaccination in this study population can be estimated by the calculations summarized in Table 7. Section A of this table shows the observed numbers of cases among reactors and nonreactors. The estimated numbers of cases without any vaccination—the potential problem—are shown in section B. To obtain the numbers of cases if all nonreactors had been vaccinated, it is only necessary to multiply the number of nonreactors by the rates observed among the vaccinees and to add this estimated number to the cases observed among reactors. The results of this calculation are shown in section C. The potential effect of a complete vaccination program is then summarized in section D, which shows the numbers

TABLE 2—Cases of Tuberculosis among Reactors and Nonreactors (with Effect of Vaccination Removed)

Tuberculin Status on Entry	Tuberculosis Cases	
	Number	%
Total	1,976	100.0
Reactors	1,400	70.9
Nonreactors	576*	29.1
Refusals	174	
Controls	141	
Vaccinees	261*	

* Estimated as explained in text.

TABLE 4—Incidence of Tuberculosis among Controls and Vaccinees

Study Category	Population	Tuberculosis Cases*	
		No.	Average annual rate/100,000
Controls	27,338	141	27.6
Vaccinees	50,634	186	19.7

* Percentage reduction in tuberculosis among vaccinees: 28.7.

TABLE 3—Total Tuberculosis Cases, and Number and Percentage of Cases Arising from Nonreactors (with Effect of Vaccination Removed) by Initial Age Group and by 5-Year Period of Observation

Years of Observation	Total			Age Group								
				1–6			7–12			13–18		
	Total cases*	Nonreactors*		Total cases*	Nonreactors*		Total cases*	Nonreactors*		Total cases	Nonreactors*	
		No.	%		No.	%		No.	%		No.	%
Total	1,976	576	29.1	231	112	48.5	789	269	34.1	956	195	20.4
0–4	757	182	24.0	104	42	40.4	217	72	33.2	436	68	15.6
5–9	656	169	25.8	60	33	55.0	279	70	25.1	317	66	20.8
10–14	370	144	38.9	45	26	57.8	207	87	42.0	118	31	26.3
15–19†	193	81	42.0	22	11	50.0	86	40	46.5	85	30	35.3

* Numbers estimated as explained in text.

† Incomplete period.

TABLE 5—Average Annual Incidence of Tuberculosis per 100,000 among Controls and Vaccinees, by Age, Sex, Race, and Place of Residence

	Controls			Vaccinees			
		Cases			Cases		
	Person-years	No.	Rate*	Person-years	No.	Rate*	% Reduction
Total	510,708	141	27.6	944,559	186	19.7	28.7
Initial age							
1–6	111,214	32	28.8	243,856	50	20.5	28.7
7–12	265,833	63	23.7	461,929	73	15.8	33.3
13–18	133,661	46	34.4	238,774	63	26.4	23.3
Sex							
Male	243,250	78	32.1	453,678	80	17.6	45.0
Female	267,458	63	23.6	490,881	106	21.6	8.5
Race							
White	451,501	122	27.0	838,879	162	19.3	28.5
Nonwhite	59,207	19	32.1	105,680	24	22.7	29.2
Place of residence							
Urban	197,151	63	32.0	345,762	64	18.5	42.1
Rural	313,557	78	24.9	598,797	122	20.4	18.1

* Average annual rate per 100,000 population.

TABLE 6—Cases of Tuberculosis and Percentage Reduction Attributable to Vaccination, by 5-Year Periods of Observation

Period of Observation	Number of Cases		
	Controls	Vaccinees*	Reduction
0–4	47	58	33.3
5–9	39	63	12.8
10–14	35	39	39.8
15–19*	20	26	29.8

* Incomplete period.

of cases preventable by vaccination of all nonreactors. Less than 9 per cent of all potential cases in this population could have been prevented by a complete vaccination program.

The public health usefulness of BCG vaccination appeared to be greatest among the youngest age groups. Although the effectiveness of BCG vaccination among nonreactors did not differ significantly among the three age groups, the younger children were more likely to be nonreactors initially. As a consequence, a higher proportion of their subsequent tuberculosis problem arose among the initial nonreactors and thus could be affected by BCG vaccination.

Severity of Disease

In theory, prophylactic vaccination can protect not only by preventing the development of disease but also by modifying the host's response to infection so that any disease that may develop will be less severe. The classification of tuberculosis known to have developed among the study population is shown in Table 8 according to the most serious diagnosis reported during the study period. As a group, vaccinees had less serious tuberculosis than controls, but the differences were slight and could easily have occurred by chance. However, reactors differed significantly from nonreactors with respect to the types of disease that developed subsequently. The proportion of persons diagnosed as primary tuberculosis and pleural effusion was significantly higher among nonreactors than among reactors; the proportion with moderately advanced pulmonary tuberculosis was lower among nonreactors. No significant differences were noted in the case fatality rates.

Age-adjusted tuberculosis death rates were highest among the initial tuberculin reactors, ranging from 11.6 per 100,000 per year among reactors with 16 mm or more induration to 4.2 among those with 6 to 10 mm of induration. The rates among nonreactors were lower: 1.6 for refusals, 2.6 for controls, and 1.6 for vaccinees.

For nontuberculous causes, the age-adjusted average annual death rates were slightly higher among reactors than among nonreactors, 60.2 per 100,000 compared with 52.8. The nontuberculous death rates were almost identical for control and vaccinees, 52.2 and 51.3 respectively, and only slightly higher for refusals, 54.8.

Discussion

The controlled trials of BCG vaccination conducted by the U.S. Public Health Service have shown that the two basic assumptions needed for the valid use of BCG vaccination as a public health procedure do not hold for the

TABLE 7—Recapitulation of the Potential Usefulness of BCG Vaccination, by Age Groups

	Age Group			
	Total	1–6	7–12	13–18
A. Observed cases:				
Total	1,901	211	752	938
Reactors	1,400	119	520	761
Nonreactors	501	92	232	177
B. Tuberculosis problem: estimated cases if NO nonreactors had been vaccinated:				
Total	1,976	231	789	956
Reactors	1,400	119	520	761
Nonreactors	576	112	269	195
C. Estimated cases if ALL nonreactors had been vaccinated:				
Total	1,802	201	696	905
Reactors	1,400	119	520	761
Nonreactors	402	82	176	144
D. Cases that could have been prevented if all nonreactors had been vaccinated:				
Number	174	30	93	51
% of tuberculosis problem	8.8	13.0	11.8	5.3

TABLE 8—Classification of Cases by Tuberculin and Vaccination Status

Classification of Cases	Tuberculin and Vaccination Status									
	Total		Reactors		Refusals		Controls		Vaccinees	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total cases	1,901	100.0	1,400	100.0	174	100.0	141	100.0	186	100.0
Pulmonary	1,733	91.2	1,286	91.9	152	87.4	127	90.1	168	90.3
Far advanced	466	24.5	344	24.6	43	24.7	38	27.0	41	22.0
Moderately advanced	605	31.8	466	33.3	53	30.5	36	25.5	50	26.9
Minimal	508	26.7	389	27.8	44	25.3	30	21.3	45	24.2
Primary	134	7.0	73	5.2	12	6.9	19	13.5	30	16.1
Stage unknown	20	1.1	14	1.0			4	2.8	2	1.1
Nonpulmonary	151	7.9	102	7.3	21	12.1	14	9.9	14	7.5
Meningeal, miliary	26	1.4	20	1.4	2	1.1	2	1.4	2	1.1
Genitourinary	12	0.6	8	0.6	2	1.1	1	0.7	1	0.5
Bone and joint	17	0.9	12	0.9	3	1.7			2	1.1
Gastrointestinal	1	0.1	1	0.1						
Lymphadenitis	69	3.6	48	3.4	9	5.2	6	4.3	6	3.2
Pleural effusion	26	1.4	13	0.9	5	2.9	5	3.5	3	1.6
Not specified	17	0.9	12	0.9	1	0.6			4	2.2
Tuberculosis deaths*	130	6.8	100	7.1	10	5.7	12	8.5	8	4.3

* Included in total cases.

United States. In contrast to widely held views in 1950, most of the subsequent tuberculosis in this country has arisen from persons infected in the distant past, and neither of the two BCG strains used in the trials was particularly effective in preventing tuberculosis among the uninfected. The question naturally arises whether there were at that time any clues which, in the light of present-day knowledge, might now make the outcome more predictable? Faced with a similar situation today, what preliminary investigative procedures should be recommended and what inferences might be drawn from them?

First of all, it should have been clear even then that the proportion of the tuberculosis case-load arising among newly infected persons depends on the risk of becoming infected with tubercle bacilli. With no chance of becoming infected, all subsequent tuberculosis would come from persons who were already infected. Conversely, with a high risk of infection, a considerable proportion of cases would

come from persons who at the start of observation were yet to be infected. In this study population, the prevalence of infection as indicated by tuberculin testing was high. However, the slight upward concavity of the age-prevalence curve should have afforded some inkling that the rate of infection might be decreasing.

Furthermore, the high proportion of persons with relatively low grade tuberculin sensitivity would now indicate that a significant proportion of the reactors might be infected with something other than *Mycobacterium tuberculosis.* Such a finding should suggest dual testing with PPD-tuberculin and PPD's from the atypical mycobacteria as a means of estimating what proportion of the tuberculin reactions might have resulted from tuberculous infections.[8] From the vantage point of hindsight, it seems entirely possible that a significant proportion of tuberculin reactors, especially among younger children, might have been infected with something other than tubercle bacilli. In that case, the age-prevalence curve of "true" tuberculous infections would have been more markedly concave upward, a finding suggestive of a rapidly falling risk of infection. A low and rapidly falling risk of infection in turn indicates that most future cases of tuberculosis will come from persons who had already been infected at that time.

In addition to improving the estimate of the proportion of cases arising from newly infected persons, the technique of dual testing with PPD-tuberculin and another PPD might have indicated that even a potent strain of BCG might not be very effective in preventing tuberculosis among nonreactors to 10 TU of tuberculin. It has been clearly shown that infections with some atypical mycobacteria confer protection against tuberculosis and that such infections diminish the usefulness of BCG vaccination among experimental animals.[9] Evidence of the protective effect of atypical infections has also been found in man.[8] Unfortunately, the findings of the present study do not add support to this view. If infections with atypical mycobacteria had had a protective effect in Puerto Rico, the case rates among persons with no reaction to 100 TU of tuberculin should have been higher than among those with low grade tuberculin sensitivity. In fact, they were essentially the same. However, too little is known about the atypical mycobacteria causing infections in man to rule out the possibility that strains prevalent in some areas may confer protection against tuberculosis while those in other areas may not.

Nor was there any indication that the presence of low grade tuberculin sensitivity interfered with the effectiveness of BCG vaccination in reducing tuberculosis among the nonreactors to 10 TU of tuberculin. The percentage reduction attributable to vaccination was essentially the same for persons with no induration, small reactions, and moderate to large reactions to the 100 TU test. This finding, plus the results of a controlled trial of BCG vaccination among children in Muscogee County, Georgia,[2,3] indicates that selection of persons for vaccination by the use of the 100 TU test would not succeed in improving its effectiveness, contrary to the suggestion of some critics.[10]

Questions about the potency of the strains of BCG used in various controlled trials cannot be answered satisfactorily at this time, and perhaps never can be. Only the two vaccine strains then available for widespread use in this country were selected for testing in the U.S. Public Health Service trials because it seemed pointless to test any others. At the time of their use, both strains were judged to be acceptable on the basis of currently available studies. Some time later, tests by other investigators suggested that the Tice-Chicago strain used in Muscogee County, Georgia, and Russell County, Alabama, was severely attenuated, and the Birkhaug-Albany strain used in Puerto Rico was moderately attenuated.[11] However, recent comparative ratings of BCG vaccines by a number of laboratories have shown striking disagreements in the assessment of potency based on animal experiments.[12] This work raises serious doubts about the results of animal tests in the past, while pointing the way toward more reliable animal testing in the future.

The use of postvaccinal conversion rates to assess the potency of BCG vaccines is also highly dubious. Low grade tuberculin sensitivity may result in false estimates of postvaccinal conversion rates.[13] More direct evidence of the inability of postvaccinal sensitivity to predict subsequent protection against tuberculosis can be obtained by comparing the results of a number of controlled trials. No correlation of protection with postvaccinal conversion rates can be found.[14]

The past performance of BCG vaccines in controlled trials among human populations might be expected to provide the best clue to present potency. Aside from the fact that only a few strains have been tested in this way, the long lapse of time since these trials were initiated causes uncertainty about current vaccine potency. The three strains used in the four major trials started around 1950 were associated with markedly different rates of reduction in tuberculosis attributable to vaccination. The Tice-Chicago strain gave very little protection in Georgia and Alabama,[15] the Birkhaug-Albany strain gave low protection in Puerto Rico, and the Danish strain gave moderate protection in South India[16] and high protection in England.[17] Because all three strains originally came from the same parent strain, any changes in potency must have resulted from environmental circumstances associated with their long residences in different laboratories. It is now more than 20 years since these strains have been tested in man. Who can say that their potency today would be rated similarly?

In spite of widespread evidence to the contrary, voices are still raised in favor of BCG vaccination on the assumption that certain population groups have a high risk of becoming infected with tubercle bacilli. If the experience of the Puerto Rico trial has accomplished nothing else, it should emphasize the desirability of estimating as carefully as possible the actual risk of infection before plunging into a vaccination program that could make subsequent estimates of the infection rate impossible. High tuberculosis case rates and low risks of acquiring new infections can coexist in the same population.[18] In such circumstances,

BCG vaccination could do little good and much harm by interfering with the identification of infected persons.

Faced with a situation today similar to that found in Puerto Rico 20 years ago, it is clear that much could be done to estimate the need for vaccination but that almost nothing could be done to ensure that a potent vaccine could be selected. A major lesson of the past 20 years—that the effectiveness of BCG vaccination in various circumstances can range from 80 per cent down to 0 per cent—seems to have gone unheeded by most of the world's tuberculosis workers. Time and time again one hears that BCG can give 80 per cent protection, with the implicit assumption that any strain used in any situation will live up to this expectation. It seems much more likely that some of the world's BCG strains are virtually useless, some confer moderate protection, and some—perhaps only a few—are highly potent. Which is which cannot at present be told. Because BCG vaccination is the major method of tuberculosis control in all but a few highly developed nations, it is particularly tragic that the use of scarce resources to administer BCG must still be based on blind faith.

Summary

In 1949—1951, 191,827 children 1 to 18 years of age were enrolled in a controlled trial of BCG vaccination in Puerto Rico. The trial was conducted as similarly as possible to a mass vaccination campaign. Follow-up, which was continued until 1969, utilized official reports of tuberculosis to avoid bias and to yield figures comparable to usual tuberculosis statistics. Among the 1,976 cases estimated to have occurred without vaccination, 29 per cent were nonreactors to 10 TU of tuberculin and hence were eligible for vaccination. Although vaccination resulted in a 29 per cent reduction in tuberculosis among nonreactors, the overall reduction in tuberculosis that would have resulted from a complete vaccination program was less than 9 per cent. Vaccination did not reduce the severity of cases that occurred among nonreactors. Screening with 100 TU of tuberculin would not have resulted in a significantly different estimate of the effectiveness of BCG.

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