Tuberculosis Studies in Muscogee County, Georgia

Twenty-year evaluation of a community trial of BCG vaccination

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PROTECTION of the uninfected was a major concern of the Tuberculosis Control Program of the Public Health Service in 1950. The belief that most tuberculosis in this country was coming from persons who had recently been infected was then still generally accepted, and the time-honored method for control was to attempt to find and isolate the person with an infectious case as early as possible in the course of his disease. This method was like locking the barn after the horse has been stolen. Although it was better to isolate the infectious person then rather than never, many contacts had often already become infected by the time the index case was diagnosed.

A preventive measure, such as active immunization, that conferred protection before exposure had obvious appeal. Other communicable diseases had been brought under control when active immunization supplanted casefinding and isolation of patients. Support for active immunization as a method of preventing tuberculosis was brought to a focus in the United States by the mass BCG vaccination campaigns being conducted at this time by the World Health Organization in many war-ravaged countries. If BCG vaccination proved as effective as its proponents claimed, it might be the ideal lock for the barn door.

Because it seemed prudent to test BCG before embarking on a mass campaign in this country, the Public Health Service undertook a series of systematic studies, including controlled trials on human populations (*1*). The first was conducted in 1947 among school children in Muscogee County, Ga., where the tuberculosis problem seemed similar to that for the United States as a whole (*2*). Two years later, a much larger trial was started among children in Puerto Rico, where tuberculosis rates were then very high (*3*). At this time, early results from the Muscogee County trial suggested that not much tuberculosis could be expected among school children whose tuberculin tests showed that they were not infected at the start of the trial. Consequently, a much more extensive trial was planned for Muscogee County and for its neighbor across the Chattahoochee River in Alabama, Russell County. It was hoped that the protection of uninfected adults by BCG vaccination would have a more immediate effect on tuberculosis than the vaccination of school children, who for the most part were in the so-called "golden years" between early childhood and adolescence, a period when children appear to be resistant to the effects of tuberculosis infection.

The results of the Public Health Service third community trial, at 7 years and 14 years after its initiation, have already been reported (*4,5*). The present paper extends these results for a 20-year followup period.

Materials and Methods

During 4 months in the first half of 1950, a mass tuberculin testing and chest photofluorographic survey was conducted in Muscogee County and Russell County. All residents of the two counties over the age of 5 years were eligible, a total of 137,503 persons according to the 1950 census. Slightly more than half of the eligibles participated. At the initial examination, 5 tuberculin units (TU) of purified protein derivative (PPD) of tuberculin were given intracutaneously. The PPD was lot RT 19–20–21 from the Statens Seruminstitut of Copenhagen, Denmark.

Three days after testing, the skin test sites were carefully examined, and the transverse diameter of any induration was recorded in millimeters. Persons with an

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induration measuring 5 or more mm were called reactors. Nonreactors were divided into two groups, those born in odd-numbered years and those born in even-numbered years. One group was offered BCG vaccination; the other was left unvaccinated as controls. A few persons who should have been vaccinated but were not because of refusals, medical contraindications, or errors and the persons who were vaccinated by mistake were called irregulars. Persons with chest photofluorograms considered by either of two film readers to show pulmonary abnormalities and persons with a history of tuberculosis were excluded from the study population regardless of the skin test results. After these exclusions, the total study population was 64,136 persons, of whom 29,369 were reactors, 17,854 were controls, and 16,913 were vaccinees.

BCG vaccine (Tice strain) was obtained from Dr. S. R. Rosenthal of the Research Foundation, Chicago, Ill. It was kept refrigerated until its use on the 3d to 5th day after preparation and was protected against sunlight and heat. The vaccine was given by multiple tangential acupuncture.

No special followup procedures were used for the study population. Tuberculosis cases came to the attention of the two county health departments in the usual ways, although it should be noted that casefinding procedures were more extensively applied in this community than in most other areas. Virtually all tuberculosis cases and suspected cases were initially detected by chest photofluorography. If a diagnosis of definite or suspected tuberculosis was made on the basis of a person's initial or followup examination (which included a full-sized chest roentgenogram), the person's name was listed in the county tuberculosis case register. A name was also occasionally entered as the result of a postmortem examination. Records of persons diagnosed as having definite or suspected tuberculosis were matched against the list of persons who had participated in the 1950 BCG trial.

In 1964, a sample of 1,113 participants was investigated to determine their current residence. On the basis of this sample, it was estimated that approximately 75 percent of the study population were still residing in the two counties at the midpoint of the observation period. There were no significant differences in the percentage of persons still in the area by age, sex, race, or tuberculin and vaccination status in the trial. Followup was discontinued as of April 1, 1970; the average period of observation was thus 20 years. Prolonged followup was greatly facilitated by the cooperation of chest clinic personnel of the Muscogee and Russell County Health Departments.

Results

During the 20-year observation period, the names of 550 of the 64,136 persons in the initial study population were recorded in the tuberculosis case registers of Muscogee and Russell Counties, either as having tuberculosis or as being suspects. Their initial tuberculin and vaccination status and their final classifications are shown in table 1. By far the greatest number, 377, were persons who had reacted in 1950 to 5 TU of PPD with 5 or more mm of induration. Approximately equal numbers were controls and vaccinees—82 controls and 80 vaccinees. Eleven were persons who had completed tuberculin tests and who had negative chest photofluorograms, but who for various reasons did not meet the criteria for reactors, controls, or vaccinees.

Table 1. Distribution of cases by screenees' final diagnostic category and initial tuberculin and vaccination status

Final diagnostic category	Initial tuberculin and vaccination status			
	Reactors	Nonreactors		
		Controls	Vaccines	Irregulars
Total cases	377	82	80	11
Confirmed tuberculosis ...	164	29	27	4
Presumptive tuberculosis ..	43	7	5	0
Suspected tuberculosis ...	133	35	36	4
Nontuberculous	37	11	12	3

Table 1 indicates the last known diagnostic category of the participants who had been listed in the case registers. The persons shown as having confirmed cases were those from whom tubercle bacilli had been isolated, or in a few instances, those persons whose diagnoses were based on necropsy examinations. The persons shown as having presumptive cases lacked such confirmation but at the time of their diagnosis had indurations to 5 TU of PPD measuring 10 or more mm in diameter and in addition either had lesions consistent with tuberculosis that were demonstrable on chest roentgenograms (other than isolated calcified nodules) or had a clinical diagnosis of nonpulmonary tuberculosis. Persons with nontuberculous cases were those who upon subsequent examination gave substantial evidence that they did not have tuberculosis. Persons shown as having cases of suspected tuberculosis were those with abnormalities that could be tuberculous (other than isolated calcified nodules) but who did not meet the criteria for the other groups. Because the Muscogee County tuberculosis study was originally set up to evaluate the long-term prognosis of pulmonary lesions that resembled tuberculosis, no one was discharged as nontuberculous on the basis of a negative tuberculin test. The category of persons with suspected cases was therefore undoubtedly heavily loaded with persons who never had had tuberculosis.

A fundamental issue was how to define a case of tuberculosis for the analysis. Because the status of participants in the 1950 BCG trial was entered on their case

records after the case register cards were made out, from that time on, clinicians could learn whether or not a vaccination had been done. Up to this point, diagnosis had been blind; after this point, it was not. Thus, the initial classification of the total group of persons in table 1 as having definite or suspected tuberculosis was unbiased. It is possible, however, though not likely, that allocation to the various final categories could be biased. Fortunately, in assessing the effectiveness of BCG vaccination, it makes little difference which categories are counted in the analysis as having cases. Combining the confirmed and the presumptive categories to form the group of study cases has two advantages: (*a*) this combination corresponds to the cases officially reported to the State health departments and (*b*) it results in the most favorable outcome for BCG of any of the reasonable combinations of categories.

Cases classified as irregular on the basis of the persons' initial examinations also present a problem. Irregulars, for the most part, were persons who would have been vaccinated had they not refused or were persons who had medical contraindications to vaccinations. Omission of these persons from the analysis, as has been done in this report, again tips the scales slightly in favor of BCG.

The average annual case rate over the 20-year period is shown in table 2 according to the initial tuberculin and vaccination status of the subjects. The rate among all reactors was 3.5 times greater than that among controls. Among persons whose tuberculin induration measured 10 mm or more initially, the rate was 73.2 per 100,000 per year, 5.5 times greater than the control rate. Vaccinees had a rate of 12.6, only 6 percent lower than the control rate of 13.4—a reduction that could easily have occurred by chance.

Table 2. Average annual incidence of tuberculosis per 100,000 screenees, by initial tuberculin and vaccination status

Initial tuberculin and vaccination status	Estimated midpoint population	Cases	Average annual incidence
Reactors	22,027	207	47.0
5–9 mm induration	13,148	77	29.3
10–14 mm induration	6,234	88	70.6
15–19 mm induration	2,210	36	81.4
20 mm or more induration	435	6	69.0
Controls	13,390	36	13.4
Vaccinees	12,685	32	12.6

It is difficult to assess time trends in the incidence of tuberculosis in the study population because of the small numbers of cases among the nonreactors to tuberculin. There is a decided downward trend among the reactors, especially after the first 5-year period, but no discernible trend among the controls or vaccinees (table 3). At no period, is there a statistically significant difference in case rates between controls and vaccinees.

The classification of study cases by the most serious diagnosis during the observation period is shown in table 4. The great majority of the cases, 88 percent, were classed as pulmonary; 73 percent of these pulmonary cases were advanced. The controls had slightly less advanced disease than the other groups, but this difference could have occurred by chance. A striking, but not entirely unexpected, result in a population in which new infections were rare was that 11 of 13 cases of miliary and meningeal tuberculosis occurred among persons who had been reactors in 1950. The remaining two cases occurred among vaccinees.

Discussion

During the first 12 years of this study, casefinding efforts in both the county health departments studied were unusually extensive, partly because the Public Health Service contributed personnel, services, and funds to the Muscogee County tuberculosis study. With the decrease in Federal funding for this type of research facility, casefinding came to be supported entirely by local and State funds. Any resulting changes, however, in the extent and character of casefinding during the later years of the study are unlikely to have affected the observed case rates much. Most of the study population with cases had manifest disease and would likely have come to attention as long as diagnostic facilities remained available. What is more significant is that there is no reason to

Table 3. Average annual incidence of tuberculosis per 100,000 screenees, by years since trial and initial tuberculin status

Years since trial	Reactors			Controls			Vaccinees		
	Midpoint population	Cases	Case rate	Midpoint population	Cases	Case rate	Midpoint populations	Cases	Case rate
0–4	27,595	79	57.3	16,776	13	15.5	15,891	7	8.8
5–9	24,050	69	57.4	14,621	8	10.9	13,850	10	14.4
10–14	20,505	37	36.1	12,466	12	19.3	11,809	9	15.2
15–19	16,961	22	25.9	10,311	3	5.8	9,767	6	12.3

Table 4. Type of tuberculosis by screenees' initial tuberculin and vaccination status

Type of tuberculosis	Reactors	Controls	Vaccinees
Total cases	207	36	32
Pulmonary	182	32	28
Far advanced	68	6	15
Moderately advanced	63	15	9
Minimal	48	8	3
Primary	...	2	...
Stage unknown	3	1	1
Nonpulmonary	25	4	4
Miliary, meningeal	11	...	2
Genitourinary	4	2	...
Pleurisy with effusion	4	1	...
Lymph node	3	1	1
Bone and joint	2	...	...
Pericardial	1	...	1

suspect that changes in casefinding could have affected reactors, controls, and vaccinees differently.

As the risk of becoming infected with tubercle bacilli becomes very low, errors in classifying persons as reactors or nonreactors to tuberculin could have an increasingly greater effect on the estimates of subsequent case rates among nonreactors and, indirectly, on the estimates of the reduction in tuberculosis attributable to BCG vaccination. Assume for a moment that in this study population absolutely no persons became infected with tubercle bacilli after entry into the trial. All cases among initial nonreactors—controls and vaccinees alike—would then have arisen among infected persons who had been classified by the tuberculin tests as nonreactors. The rates among controls and vaccines would have been low, and except for random variations, equal. No matter what the inherent protective power of BCG might be, it apparently would be completely ineffective in such a situation.

Studies of the tuberculin sensitivity of hospitalized tuberculosis patients have often shown that approximately 5 percent have less than 5 mm of induration to 5 TU of PPD (*6*). It would therefore be conservative to assume for the sake of argument that as many as 10 percent of the true reactors in this study population had been falsely classified as nonreactors. Such an estimate leads to the conclusion that there would have been 2,447 reactors among the midpoint population of nonreactors—1,257 among the controls, and 1,190 among the vaccinees. If these false nonreactors had had the same case rate as the reactors, namely 47 per 100,000 per year, 12 of the control cases and 11 of the vaccinee cases would have arisen among them. Subtracting these cases from the observed cases allows estimates of the "true" average annual case rates among controls of 9.9 and among vaccinees of 9.1—a reduction of 8 percent attributable to BCG. It is thus clear that no reasonable assumptions about misclassification of reactors can account for the poor performance of BCG vaccination in this population.

It is also possible that infections with nontuberculous mycobacteria might have provided so much natural protection that there was no room for further protection by BCG. Clearly, some strains of nontuberculous mycobacteria produce considerable protection in animals, although usually not as much as some strains of BCG (*7*). There is also suggestive evidence that such protection occurs in man (*8*). However, to produce case rates in the control group nearly as low as those among the vaccinees would require that such infections be nearly universal and, moreover, that they be nearly as potent as BCG. The first condition may have been present in Muscogee and Russell Counties. Studies of Navy recruits from this general area have shown that more than 80 percent of them reacted to at least one skin test antigen prepared from nontuberculous mycobacteria (*9*). But the other condition, namely that the infecting organism must be nearly as potent as BCG, seems unlikely to be fulfilled on the basis of current evidence. Most nontuberculous mycobacteria give rather weak protection in animals (*7*); they would give protection similar to that afforded by BCG only if the particular strain of BCG was not very potent.

Claims have been made that the BCG vaccine used in this trial was low in protective power, even though at the time of use it was generally regarded as potent and was a duly licensed biological product (*10*). Unfortunately, the relative potency of the Tice strain of BCG in this trial cannot now be assessed with certainty. However, animal tests have suggested that variations in its potency occurred after the date of this trial (*11*), and only one of four trials in humans has indicated that it afforded a satisfactory degree of protection (*2,5,12,13*).

At present, the situation with respect to the BCG vaccine is reminiscent of the status of the pertussis vaccine in the early 1960s. At that time there was considerable uncertainty both as to the efficacy of pertussis vaccine and of the ability of animal tests to evaluate it. The situation was clarified by conducting a controlled trial of pertussis vaccine in humans, thereby identifying a potent vaccine, and then using that vaccine to demonstrate which animal tests were reliable indicators of the vaccine's potency (*14*).

At present, there is reason to question the efficacy of current BCG vaccines. Almost none of the available strains have been tested in a controlled trial, and the few that have been tested have been subcultured for so long that one cannot be certain that they still possess their original potency. Tuberculin conversion, long considered a field test of vaccine effectiveness, does not correlate with protection against tuberculosis (*15*). Also, recent work has indicated much disagreement about various procedures for testing the potency of BCG in animals

(*16*). As was the case with pertussis vaccines 20 years ago, the only resolution of the present uncertainties about BCG strains seems to lie in setting up controlled trials among humans of the currently available strains in areas of the world where the risk of infection is still sufficiently high to indicate a need for BCG vaccination and also high enough to yield an answer in a reasonable length of time.

In such trials, vaccinated persons need not be compared with randomly allocated unvaccinated controls, although such a design is scientifically desirable and is the basis of a current study supported by the Government of India, the Public Health Service, and the World Health Organization (*15*). For practical purposes, even a much simpler scheme should be useful and would be more widely applicable. If several different BCG strains were used in a country with high rates of infection and each strain was tested in a different region, a comparison of tuberculosis trends before and after vaccination with the trial strains could separate the highly potent strains from the weak if a reasonable effort were exerted to maintain similar levels of vaccination and casefinding in all regions. A few such studies might allow a number of BCG vaccines to be ranked in the order of their potency, thereby providing material with which to identify reliable animal test systems. Once such a test system was found, objective ratings of the BCG vaccines could be done. Tuberculosis control personnel working in areas of the world where protection by vaccination is still needed could then learn whether or not they were using an effective vaccine and would not have to proceed on faith alone, as they must do at present.

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SYNOPSIS

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A controlled trial of BCG vaccination was conducted in 1950 in Muscogee County, Ga., and Russell County, Ala. The study population consisted of 64,136 volunteers over the age of 5 years who had satisfactory skin tests with 5 tuberculin units of purified protein derivative and whose chest photofluorograms were considered by two readers to show no significant pulmonary abnormalities. Approximately half of the nonreactors to tuberculin were vaccinated with the Tice strain of BCG by a multiple-puncture method.

During a 20-year period of follow-up, 207 cases of tuberculosis were identified among the persons who had been tuberculin reactors in 1950, 36 cases were identified among the controls, and 32 cases were identified among the vaccinees. The average annual case rates per 100,000 were 47.0 for reactors, 13.4 for controls, and 12.6 for vaccinees.