Long-term Efficacy of BCG Vaccine in American Indians and Alaska Natives
A 60-Year Follow-up Study

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BACILLE CALMETTE-GUÉRIN (BCG) is an attenuated strain of *Mycobacterium bovis* that is used worldwide as a tuberculosis vaccine. Although the reported efficacy of BCG vaccines in controlled trials varies greatly, a meta-analysis found that overall, the vaccine reduced the risk of tuberculosis by 50% but that the duration of the protective effect could not be quantified.[1] A meta-analysis of efficacy over time among randomized controlled trials reported a 5% to 14% annual decrease among 7 trials and an increase in efficacy of up to 18% among 3 others.[2]

More than 50 years ago, Townsend et al[3] conducted a placebo-controlled trial of BCG vaccination among American Indians and Alaska Natives. Immunizations for this study occurred during 1935-1938, with prospective tuberculosis case finding through 1947. A 20-year analysis of tuberculosis mortality found an 82% reduction attributable to vaccination[4]; there was a 75% reduction in radiographically diagnosed tuberculosis at 11 years.[5]

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The original American Indian vaccine trial documents have been preserved over the intervening decades. Since study participants tend to obtain health care through a single system, the Indian Health Service (IHS), and to maintain ties to discrete communities, good follow-up is facilitated. We conducted a long-term follow-up of trial participants using medical record review and supplemental methods to address duration of tuberculosis protection by BCG vaccine.

Context The duration of protection from tuberculosis of BCG vaccines is not known.

Objective To determine the long-term duration of protection of a BCG vaccine that was previously found to be efficacious.

Design Retrospective record review using Indian Health Service records, tuberculosis registries, death certificates, and supplemental interviews with trial participants.

Setting and Participants Follow-up for the period 1948-1998 among American Indians and Alaska Natives who participated in a placebo-controlled BCG vaccine trial during 1935-1938 and who were still at risk of developing tuberculosis. Data from 1483 participants in the BCG vaccine group and 1309 in the placebo group were analyzed.

Main Outcome Measures Efficacy of BCG vaccine, calculated for each 10-year interval using a Cox regression model with time-dependent variables based on tuberculosis events occurring after December 31, 1947 (end of prospective case finding).

Results The overall incidence of tuberculosis was 66 and 138 cases per 100 000 person-years in the BCG vaccine and placebo groups, respectively, for an estimate of vaccine efficacy of 52% (95% confidence interval, 27%-69%). Adjustments for age at vaccination, tribe, subsequent BCG vaccination, chronic medical illness, isoniazid use, and bacille Calmette-Guérin strain did not substantially affect vaccine efficacy. There was slight but not statistically significant waning of the efficacy of BCG vaccination over time, greater among men than women.

Conclusion In this trial, BCG vaccine efficacy persisted for 50 to 60 years, suggesting that a single dose of an effective BCG vaccine can have a long duration of protection.

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METHODS

Summary of BCG Vaccine Trial

Details of the original BCG vaccine trial have been published previously.[3-10] In summary, between December 1935 and February 1938, 3025 American Indian and Alaska Native children and adults aged 1 month to 20 years who had normal chest radiographs and who did not react to a strong dose (approximately 250 TU) of purified protein derivative of tuberculin were allocated to receive either a single intracutaneous dose of BCG vaccine or normal saline as a placebo. The trial was conducted in southeast Alaska, Arizona, North Dakota, South Dakota, and Wyoming. Allocation to vaccine or placebo group was by systematic alternation after stratification by school, age, and sex. Until the current follow-up in the 1990s, participants were not aware to which study group they had been allocated; the investigators of the original trial were not blinded. Two strains of BCG vaccine were used: strain 317 obtained from Calmette (Pasteur Institute, Paris, France, 1926) via Park (New York City Health Department laboratory) via King (Mt McGregor laboratory, Mt McGregor, NY) to the Phipps laboratory, Philadelphia, Pa, in 1928; and strain 575 from Guérin (Pasteur Institute) in 1938. Strain 317 was used in a dose of 0.15 mg in lots 1 to 4 and 7 to 10 and in a dose of 0.1 mg in lots 5 and 6. Strain 575 was used in a 0.1-mg dose for lots 11 to 13 at the Alaska sites. These 13 lots of BCG vaccine were prepared from live cultures of BCG in a mobile laboratory, and the vaccine was used within 3 days of preparation. Prospective evaluation of trial participants, including chest radiography and tuberculin testing, occurred annually through 1947 except during 1945-1946.

Follow-up Study Protocol

The present follow-up of the study participants took place from 1992 to completion of data collection in 1998. Participants and their medical records were located using information from the initial study cards, with assistance from the tribal offices, the Bureau of Indian Affairs, the IHS, Sea Alaska Corp, the GeoNorth Inc database, the Social Security Death Master File, and the National Death Index.

This follow-up study was approved by the institutional review boards of Johns Hopkins Bloomberg School of Public Health, Walter Reed Army Medical Center, Uniformed Services University of the Health Sciences, IHS, Arizona Health Department, and Southeast Alaska Regional Health Corp. Participants provided oral or written informed consent for the interview process.

Information, entered onto standardized data forms, was collected without knowledge of participants' immunization status in the original trial. Sources of information were primarily the IHS medical records (both inpatient and outpatient), state and IHS tuberculosis registries, death certificates, and original study data cards, supplemented by interviews with participants from whom additional information was required. In Arizona, we obtained some data from a study of natural history of chronic diseases among the Akimel O'odham (Pima) people. Interviews were usually conducted by telephone, but in some cases, information was obtained through mailed questionnaires or face-to-face interviews. Information collected included results of tuberculin tests and chest radiography, clinical diagnoses of tuberculosis, mycobacteriology reports, autopsy and histopathology results, history of antituberculosis treatment and chemoprophylaxis, medical risk factors, subsequent BCG vaccination, and vital status.

Tuberculosis Case Definitions

Classification of tuberculosis cases was performed by 2 separate investigators (N.E.A. and L.H.H.), with disagreements adjudicated by a third (G.W.C.); all were unaware of vaccination status. Six classifications were defined: definite, probable, or possible tuberculosis (all apply to cases since January 1, 1948); tuberculosis diagnosed before 1948; insufficient data to determine whether a patient had tuberculosis; and not tuberculosis. Definite tuberculosis required culture identification of *Mycobacterium tuberculosis* from any source. Probable tuberculosis was objective evidence of clinical tuberculosis based on history and/or physical examination as well as chest radiography and/or other diagnostic tests, without other concurrent illness that could explain the findings, plus either response to antituberculosis therapy (improved symptoms and objective improvement on diagnostic tests) or evidence of acid-fast bacilli and granulomata at autopsy. Positive smears for acid-fast bacilli were inadequate for diagnosis of probable tuberculosis unless identified at autopsy. A possible tuberculosis case was one in which the participant was diagnosed as having tuberculosis after 1947 but available information was insufficient to classify the case according to the above definitions of definite and probable tuberculosis. The category of tuberculosis diagnosed before 1948 was used for any patient given this diagnosis before January 1, 1948, regardless of the documentation available to us. Tuberculosis death was the category for persons with a diagnosis of tuberculosis listed on their death certificate since December 31, 1947, or described in a death narrative or autopsy report.

Primary End Points

The primary efficacy analysis was based on time at risk of developing tuberculosis from January 1, 1948, to first tuberculosis diagnosis or to the end of the follow-up period in 1998. Only definite and probable tuberculosis cases were included in the analysis. When multiple episodes of tuberculosis were noted, the assignment of date of onset was determined by the episode with the most certain diagnosis (definite or probable cases). The present analysis is based on information obtained after January 1, 1948, because December 31, 1947, marked the end of systematic prospective case finding, for which results have been published.[4-10] Survivors who developed tuberculosis before 1948 are included in this analysis because they were considered at risk of a subsequent tuberculosis episode (based on absence of drug treatment, less strin-

gent and different diagnostic criteria prior to 1948, and limited information on earlier medical records).

Statistical Analysis

Computation of rate ratios (RRs) and exact 95% confidence intervals (CIs) and comparisons of homogeneity of RRs were made using StatXact, version 5.[11] Vaccine efficacy was computed as $(1 - RR) \times 100\%$. Demographic and clinical characteristics of treatment groups were compared using the Fisher exact test for categorical data and 2-sample t tests for continuous data (SPSS for Windows, version 11.0, SPSS Inc, Chicago, Ill). Decade-specific efficacy estimates are based on standard life-table estimates.

Vaccine efficacy over time was assessed by fitting Cox proportional hazards models for time from January 1, 1948, to diagnosis of definite or probable tuberculosis (using the PHREG procedures of SAS, version 8.0 [SAS Institute Inc, Cary, NC]). All of these models included a term for receipt of BCG vaccine and dummy variables to adjust for site (Alaska and North Dakota, the regions with the highest and lowest numbers of tuberculosis cases), and occurrence of tuberculosis before 1948. Potential waning of vaccine efficacy was assessed with a time-dependent interaction between the logarithm of failure time and BCG vaccine receipt, and differential waning by sex with another interaction term between the waning and sex terms.

RESULTS

The original study enrollment master list contained the names of 3287 participants. Participants were excluded from analysis if the original study data card was missing (n=26), they were noted to have received placebo injections with a BCG vaccine–contaminated syringe (n=12), they developed Koch phenomenon at the BCG vaccination site, suggesting prior infection (n=2), or they received neither vaccine nor placebo (n=23) or were participants only in a separate trial among neonates (n=262). These neonates were excluded because participants in that study were not randomized, different lots of BCG vaccine were used, the study was restricted to neonates, and the study was performed during a different period. Of the remaining 2963 participants who were eligible for analysis, 1540 had received BCG vaccine and 1423 had received placebo. Those who were not followed up after December 31, 1947, were excluded from the current analysis: 57 in the BCG vaccine group (56 deaths, 9 due to tuberculosis, and 1 lost to follow-up), and 114 in the placebo group (113 deaths, 55 due to tuberculosis, and 1 lost to follow-up).

The numbers of persons included in the present analysis are 1483 in the BCG group and 1309 in the placebo group. A total of 1005 participants received strain 317 and 478 received strain 575. Although 7.1% of BCG recipients and 7.3% of placebo recipients could not be located, some follow-up information was available. Persons included in this efficacy analysis were distributed by region of enrollment into the trial as follows: 376 in North Dakota, 478 in South Dakota, 384 in Wyoming, 657 in Arizona, and 897 in southeastern Alaska. Slightly more women than men were followed up since 1948 (**TABLE 1**). Preventive isoniazid was given to 17% of total persons in the BCG vaccine group compared with 15% in the placebo group (P=.10) (**TABLE 2**). There was a slightly higher prevalence of diabetes mellitus in the placebo group, at 25.7% vs 21.8% in the BCG vaccine group (P=.02).

The total number of tuberculosis cases was 102. Most cases were culture-confirmed (n=27 in the BCG group and n=63 in the placebo group); of those cases categorized as probable tuberculosis, 9 were in the BCG group and 3 in

Table 1. Characteristics of Participants and Data Sources*

	BCG Vaccine (n = 1483)	Placebo (n = 1309)
Characteristics		
Age at vaccination, median (range), y	7.6 (0.1-20.1)	7.6 (0.2-19.9)
Vaccinated <1 y of age	61 (4.1)	54 (4.1)
Male sex	705 (48)	665 (51)
Follow-up since vaccination, median (range), y	55.6 (10.3-62.9)	55.4 (10.4-62.9)
Follow-up since December 31, 1947, median (range), y	44.8 (0.4-51.5)	44.8 (0.1-51.4)
Data sources		
Medical record review	1030 (70)	932 (71)
Direct contact†	308 (21)	260 (20)
Tuberculosis registry records	268 (18)	278 (21)
Not able to locate currently	105 (7)	96 (7)
Death certificate obtained‡	480 (83)	456 (88)

*Data are expressed as No. (%) unless otherwise indicated.
†Direct contact includes telephone interviews, face-to-face interviews, or the return of a completed medical history questionnaire.
‡Percentage of total deaths are reported in parentheses.

Table 2. Prevalence of Factors Having Potential Effect on Tuberculosis Outcome at Any Time During Follow-up*

	BCG Vaccine (n = 1483), %	Placebo (n = 1309), %	P Value
Subsequent BCG vaccination†	1.3	1.5	.63
Prophylactic isoniazid	17.4	15.0	.10
Diabetes	21.8	25.7	.02
Alcoholism	27.9	27.9	.99
Malignancy	10.8	12.7	.13
Renal failure	5.7	7.3	.09

*Approximately 20% of the study population (similar in each treatment group) had insufficient data available to assess these factors. Data were also collected on human immunodeficiency virus status, organ transplantation, steroid use, silicosis, and gastrectomy; no significant differences between groups were noted.
†BCG vaccination by an outside agency after admission to the trial.

the placebo group. The case rate since 1948 in the BCG group was 66 per 100 000 person-years and in the placebo group was 138 cases per 100 000 person-years (**TABLE 3**), for an unadjusted BCG vaccine efficacy since January 1, 1948, of 52% (95% CI, 27%-69%). Adjusting for age at vaccination, sex, additional BCG vaccine doses, chronic medical illness (diabetes, alcoholism, human immunodeficiency virus infection, malignancy, transplantation, renal failure, silicosis, gastrectomy, or steroid use), subsequent isoniazid prophylaxis, tribal membership, BCG strain, and BCG dose did not substantially change the vaccine effect. Simultaneous inclusion of these variables yielded an adjusted vaccine efficacy of 55% (95% CI, 31%-77%).

Efficacy of vaccine during 10-year intervals since 1948 is shown in the **FIGURE**. Although there was considerable variability in the observed rates, there was a tendency for a slight but not statistically significant waning of the efficacy of BCG vaccine over time. This was confirmed by the Cox regression models, using either dichotomous (plus or minus half the time of maximum follow-up) or linear specifications ($P = .32$ and $P = .65$, respectively). However, there appeared to be a difference in waning by sex, with a decline for men but not for women ($P = .02$ for interaction), with men losing most of the benefit of immunization beyond 35 to 40 years after the initiation of the trial (data not shown).

Results of other trials suggested that BCG protects against disseminated disease; specifically, miliary and meningeal tuberculosis among children.[12,13] In this trial, subdividing cases since 1948 into pulmonary, extrapulmonary, and both pulmonary and extrapulmonary categories, we found pulmonary tuberculosis rates of 35 cases per 100 000 person-years in the BCG vaccine group and 73 cases per 100 000 person-years in the placebo group (efficacy, 52%; 95% CI, 14%-74%). For extrapulmonary tuberculosis, there were 9 cases per 100 000 person-years in BCG vaccine recipients and 25 cases per 100 000 person-years in the placebo group (efficacy, 63%; 95%

CI, −11% to 90%) and for cases with both pulmonary and extrapulmonary tuberculosis, the case rates were 22 and 40 per 100 000 person-years for the BCG vaccine and placebo groups, respectively (efficacy, 45%; 95% CI, −20% to 75%). Few cases of miliary and meningeal tuberculosis were identified after 1948, 2 cases occurring in the BCG vaccine group and 4 in the placebo group. Since January 1,

1948, the BCG vaccine had an efficacy of 44% (95% CI, −22% to 75%) for preventing death due to tuberculosis. Forty-six patients had more than 1 reported episode of tuberculosis (18 were categorized as definite or probable cases). Differences between the treatment groups were seen, with multiple episode rates of 4 per 100 000 person-years in the BCG vaccine group and 34 per 100 000 per-

Table 3. Number of Tuberculosis Cases and Rates per 100 000 Person-Years in 1948-1998 Among Follow-up Study Participants Given BCG Vaccine or Placebo at Start of Trial, by Baseline Characteristics
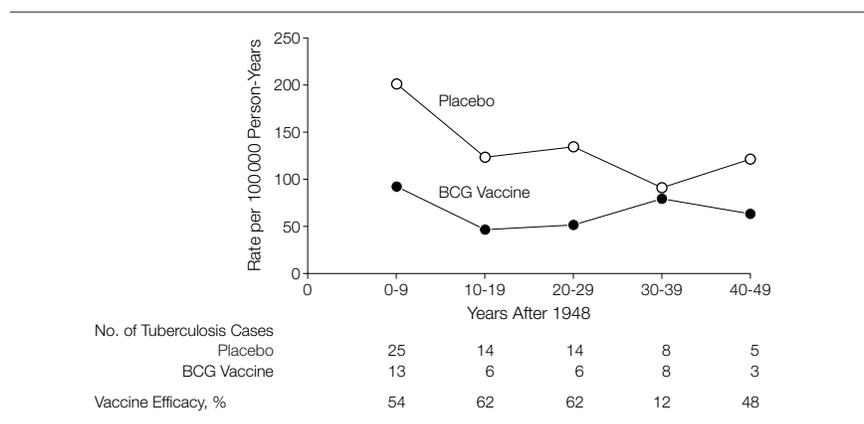
Characteristics	BCG Vaccine		Placebo		Efficacy, % (95% CI)
	No.	Rate*	No.	Rate*	
Total No. of cases	36	66	66	138	52 (27 to 69)
Sex					
Male	23	93	31	131	29 (−26 to 61)
Female	13	44	35	145	70 (42 to 85)
Location of disease					
Pulmonary	19	35	35	73	52 (14 to 74)
Extrapulmonary	5	9	12	25	63 (−11 to 90)
Pulmonary and extrapulmonary	12	22	19	40	45 (−20 to 75)
Residence at time of vaccination					
Alaska	17	93	36	227	59 (25 to 78)
Wyoming	3	37	8	136	73 (−14 to 95)
Arizona	12	103	12	106	3 (−136 to 60)
South Dakota	3	36	7	91	61 (−72 to 93)
North Dakota	1	12	3	43	71 (−262 to 99)
BCG strain					
317	19	53	30	94	44 (−3 to 70)
575	17	93	36	227	59 (25 to 78)
Cause of death					
Tuberculosis	12	22†	19	39†	44 (−22 to 70)
Other	516	935	471	958	2 (−11 to 14)

Abbreviation: CI, confidence interval.
*Based on 54 477 person-years for BCG vaccine group and 47 777 person-years for placebo group.
†Based on 55 181 person-years for BCG vaccine group and 49 182 person-years for placebo group.

Figure. Tuberculosis Incidence Rates and Efficacy by Treatment Group and Decade Since January 1, 1948

No. of Tuberculosis Cases	0-9	10-19	20-29	30-39	40-49
Placebo	25	14	14	8	5
BCG Vaccine	13	6	6	8	3
Vaccine Efficacy, %	54	62	62	12	48

son-years in the placebo group (efficacy, 89%; 95% CI, 53%-99%).

COMMENT

Wide variation has been noted in the results of controlled trials of BCG vaccine.[14] Although the efficacy of BCG vaccine in the prevention of miliary and meningeal tuberculosis among children has been noted consistently, the variable efficacy of BCG vaccines against pulmonary disease has been attributed to differences in the vaccines and/or the study populations, blunting of the apparent efficacy of the BCG response by partial protection from infection with nontuberculous mycobacteria, higher rates of exogenous exposure to tuberculosis, and varying virulence of strains of *M tuberculosis*.[14,15]

This placebo-controlled trial of BCG vaccine is the only study, to our knowledge, to demonstrate that its vaccine strains conferred a considerable degree of protection throughout most of the 60-year follow-up period. Other controlled trials of BCG vaccine have reported efficacy for follow-ups of only 15 to 20 years, and in none was a meaningful reduction in tuberculosis incidence maintained for more than 15 years.[16-28] In a review of 10 randomized BCG trials, the average efficacy more than 10 years after vaccination was 14% (95% CI, –9% to 32%).[2] A meta-analysis of BCG in neonates and infants in 3 controlled trials and 6 case-control studies indicated that BCG vaccine efficacy in this age group may persist through 10 years after vaccination.[29] In our study population, with a high incidence of tuberculosis and good follow-up rates, some waning of efficacy was observed over time, as was a decreasing number of cases in both study groups, reflecting the trends in tuberculosis in the United States during the 20th century and especially after the advent of effective antituberculosis drugs.

Strengths of this trial include use of a placebo, which was unusual among early trials of BCG vaccination, and the initial screening with a strong dose of tuberculin that should have effectively excluded any participants with nontuberculous mycobacterial infection. However, the study also has some methodological limitations. The original principal investigator was not blinded to the immunization status of the study participants. However, the participants, subsequent caregivers, and investigators for the present follow-up study were all blinded. Allocation to BCG vaccine or placebo was performed by alternation of individuals after stratification by school, year of birth, and sex, not randomly. However, we doubt that this biased the study results. It is possible that tuberculosis cases could have been undiagnosed or missed, but we believe that this should have affected both groups equally. In addition, the diagnosis of tuberculosis among American Indians has long been a major concern in this population, so we believe that frequent misdiagnosis is unlikely. Another potential problem is that immunization with BCG vaccine produces a scar, which could potentially have allowed clinicians caring for study participants over the years to know that they had received BCG vaccine. However, we do not believe that knowledge of vaccination in this trial would have substantially influenced subsequent diagnosis of tuberculosis. The number of study participants examined in the clinics serving the study areas was exceedingly small relative to the total number of patients, making it very unlikely that they would be recognized as participants or that their arms would be examined for a scar. Even if they had, the presence of smallpox vaccine scars in this population would likely have confounded the interpretation. In addition, this limitation is shared by all other studies of the effectiveness of BCG vaccination. There were gaps in the data sources for about 20% of patients. However, since this proportion was similar in both groups, this problem would have diminished the power of the study without altering the point estimate of efficacy. The CIs for most of the efficacy estimates are relatively wide. Finally, the number of tuberculosis cases in the later years was small, which limits our ability to precisely estimate efficacy during the final 2 decades of the study.

Two strains of BCG vaccine of essentially equivalent efficacy were used, both originating from the Pasteur Institute and separated in time by 8 years, potentially spanning the time when loss of the *mpt64* gene was noted.[30,31] Given that the American Indian trial was carried out during a time when live BCG vaccines had to be propagated at frequent intervals, it is not certain that additional mutations did not occur, but some BCG Phipps was later archived as ATCC strain 35744 (and is still available). Molecular phylogeny demonstrated genetic differences among BCG strains used in clinical trials, including this BCG Phipps strain.[32]

The high tuberculosis exposure rate of participants in this trial may have contributed to exogenous boosting of the BCG vaccine's protective effect over time. Unlike other US BCG vaccine trials in the 20th century, tuberculosis cases remained frequent among this American Indian and Alaska Native population, making it possible to continue to assess BCG vaccine protection. While prevalence of tuberculosis remained higher among American Indians and Alaska Natives than among the general US population, their mortality rates have fallen dramatically throughout IHS areas.[33]

The higher rates of diabetes and renal failure among the unvaccinated group are unexplained. In this population, diabetes and renal failure are closely linked, probably because most renal failure is caused by diabetes. Similar to our results, animal models of type 1 diabetes have suggested that BCG vaccine prevents insulitis and development of overt diabetes.[34,35] Other population-based studies disagree on the relative frequency of diabetes among persons vaccinated with BCG in childhood.[36-39]

The finding of differential waning of vaccine efficacy by sex is intriguing but unexplained. The pre-1948 analysis of this trial also showed that efficacy was slightly higher among women than men (79% vs 68%).[5] Sex differences in efficacy have been observed with other vaccines and, although the biological basis is not understood, it does suggest that

the difference we observed could be real.[40] However, caution is required when interpreting ad hoc subgroup analyses that address hypotheses that were not considered during the design of the study.[41] Future studies should address sex differences in BCG vaccine efficacy if the opportunity arises.

In conclusion, we report the results of a long-term controlled trial of a BCG vaccine found to have good protective efficacy against tuberculosis that extended up to 60 years after vaccination. These results should provide encouragement to investigators aspiring to produce a vaccine with similar or improved characteristics.

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