Review

Efficacy of BCG Vaccine in the Prevention of Tuberculosis

Meta-analysis of the Published Literature

Graham A. Colditz, MD, DrPH; Timothy F. Brewer, MD, MPH; Catherine S. Berkey, DSc, MA; Mary E. Wilson, MD; Elisabeth Burdick, MSc; Harvey V. Fineberg, MD, PhD; Frederick Mosteller, PhD

Objective.—To quantify the efficacy of BCG vaccine against tuberculosis (TB).

Data Sources.—MEDLINE with index terms *BCG vaccine*, *tuberculosis*, and *human*. Experts from the Centers for Disease Control and Prevention and the World Health Organization, among others, provided lists of all known studies.

Study Selection.—A total of 1264 articles or abstracts were reviewed for details on BCG vaccination, concurrent vaccinated and unvaccinated groups, and TB outcome; 70 articles were reviewed in depth for method of vaccine allocation used to create comparable groups, equal surveillance and follow-up for recipient and concurrent control groups, and outcome measures of TB cases and/or deaths. Fourteen prospective trials and 12 case-control studies were included in the analysis.

Data Extraction.—We recorded study design, age range of study population, number of patients enrolled, efficacy of vaccine, and items to assess the potential for bias in study design and diagnosis. At least two readers independently extracted data and evaluated validity.

Data Synthesis.—The relative risk (RR) or odds ratio (OR) of TB provided the measure of vaccine efficacy that we analyzed. The protective effect was then computed by 1−RR or 1−OR. A random-effects model estimated a weighted average RR or OR from those provided by the trials or case-control studies. In the trials, the RR of TB was 0.49 (95% confidence interval [CI], 0.34 to 0.70) for vaccine recipients compared with nonrecipients (protective effect of 51%). In the case-control studies, the OR for TB was 0.50 (95% CI, 0.39 to 0.64), or a 50% protective effect. Seven trials reporting tuberculous deaths showed a protective effect from BCG vaccine of 71% (RR, 0.29; 95% CI, 0.16 to 0.53), and five studies reporting on meningitis showed a protective effect from BCG vaccine of 64% (OR, 0.36; 95% CI, 0.18 to 0.70). Geographic latitude of the study site and study validity score explained 66% of the heterogeneity among trials in a random-effects regression model.

Conclusion.—On average, BCG vaccine significantly reduces the risk of TB by 50%. Protection is observed across many populations, study designs, and forms of TB. Age at vaccination did not enhance predictiveness of BCG efficacy. Protection against tuberculous death, meningitis, and disseminated disease is higher than for total TB cases, although this result may reflect reduced error in disease classification rather than greater BCG efficacy.

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From the Technology Assessment Group, Harvard School of Public Health (Drs Colditz, Berkey, Fineberg, and Mosteller and Ms Burdick); the Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School (Dr Colditz); the Infectious Disease Unit, Massachusetts General Hospital (Dr Brewer), Boston; and the Infectious Disease Unit, Mount Auburn Hospital (Dr Wilson), Cambridge, Mass. Dr Brewer is the recipient of an Alfred L. Frechette Postdoctoral Research Fellowship in Public Health from the Massachusetts Health Research Institute, Boston, Mass, and a grant from the Potts Foundation, Hudson, NY.

Reprint requests to the Technology Assessment Group, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115 (Dr Colditz).

IN 1986, the number of tuberculosis (TB) cases in the United States increased for the first time since 1953.[1] Between 1986 and 1992, there were 51 700 excess cases of active TB in the United States compared with the number expected if the downward trend of 1981 through 1984 had continued.[2] The majority of these cases occurred in the age group and from geographic areas most affected by the acquired immunodeficiency syndrome. Most (69.5%) of the TB cases in 1990 occurred among racial and ethnic minorities.[3] Central Harlem in New York City had a case rate of 233 per 100 000 population in 1990, more than 20 times the national average. All told, New York City reported 15% of the nation's TB cases,[4] although it had only 2.9% of the total population.

Concurrent with the increase in incidence of TB has been a rise in multiple drug–resistant TB.[5-8] In one nosocomial outbreak on the wards that admitted patients with multiple drug–resistant TB, 22% to 50% of health care workers had tuberculin skin test conversion.[9] To date, at least nine health care workers or prison guards have developed multiple drug–resistant TB from institutional spread and five have died.[10]

In the United States, BCG vaccination is currently recommended for tuberculin-negative infants and children who have continuing exposure to isoniazid- and rifampin-resistant active TB, who cannot take isoniazid and have ongoing exposure to a case of infectious TB, or who belong to groups with rates of new *Mycobacterium tuberculosis* infection exceeding 1% per year.[11] Institutional outbreaks and the emergence of multiple drug–resistant TB are prompting the reconsideration of broadened use of BCG vaccine in the United States.[6]

Though the BCG vaccine has been in use since 1921 and approximately 3 billion doses have been given, the efficacy of the vaccine continues to be debated.[12,13] Vaccine performance in prospective trials has ranged from possibly detrimental to an 80% protective benefit. Although all 10 of the case-control studies of BCG vaccination reviewed by Smith in 1987[14] showed efficacy in preventing TB, the range of efficacy rates approximately paralleled those found in the trials (2% to 90% protection). Confidence in the efficacy of BCG vaccine was rocked by the results of the Madras trial[15] in which BCG vaccine failed to show any

Table 1.—Reports From Clinical Trials Providing Estimates of Efficacy of BCG Vaccine Against Cases of Tuberculosis (TB) and TB Death That Were Used in the Meta-analysis*

Source, y	Population		Cases of TB			TB Death		
	BCG	No BCG	BCG	No BCG	RR	BCG	No BCG	RR
Aronson,[23] 1948†	123	139	4	11	0.41	0	4	0.14
Ferguson and Simes,[40] 1949	306	303	6	29	0.20	2	9	0.22
Rosenthal et al,[42] 1960‡	231	220	3	11	0.26	0	4	0.12
Hart and Sutherland,[41] 1977	13 598	12 867	62	248	0.24	...	...	...
Frimodt-Moller et al,[45] 1973	5069	5808	33	47	0.80	...	...	...
Stein and Aronson,[44] 1953	1541	1451	180	372	0.46	...	...	...
Vandiviere et al,[43] 1973	2545	629	8	10	0.20	...	...	...
Madras,[15] 1980§	88 391	88 391	505	499	1.01	...	...	...
Coetzee and Berjak,[39] 1968‖	7499	7277	29	45	0.63	...	...	...
Rosenthal et al,[49] 1961¶	1716	1665	17	65	0.25	1	6	0.16
Comstock et al,[47] 1974	50 634	27 338	186	141	0.71	8	12	0.36
Comstock and Webster,[48] 1969#	2498	2341	5	3	1.56	...	...	...
Comstock et al,[46] 1976#	16 913	17 854	27	29	0.98	...	...	...
Aronson et al,[51] 1958**	1541	1451	...	...	...	13	68	0.18
Levine and Sackett,[50] 1948††	566	528	...	...	...	8	8	0.93
Overall RR (95% confidence interval)			0.49 (0.34-0.70)			0.29 (0.16-0.53)		

*RR indicates relative risk. Ellipses indicate data not reported.
†Infants study.
‡TB households.
§Data based on 7.5-year follow-up of entire population. We estimated the population numbers because they were not reported.
‖Miners randomized during year 3 of the trial had a truncated follow-up period; we used person-years of follow-up to estimate total sample size.
¶Non-TB households.
#Follow-up sample sizes were not reported. We assumed follow-up was comparable in BCG and no BCG groups.
**This report on deaths is based on the same trial as Stein and Aronson, 1953.[44]
††Data after 1932 recruitment.

benefit against pulmonary TB.[16] Critics of the trial point out that follow-up was at 2.5-year intervals, case detection in children was based entirely on symptoms of cough followed by sputum examination, and peak incidence was not in the usual young adult age group but in older individuals. Despite results of the Madras trial, BCG vaccination continues to be recommended by the World Health Organization (WHO) as part of the Extended Program on Immunization for infants and is used by the majority of countries in the world.[17]

Questions about BCG vaccination that remain unresolved include its overall efficacy, the duration of protective immunity, and how age at vaccination affects protection.[14,18-20] Also lacking is consistent information on the efficacy of individual strains of BCG.[19,20]

We undertook a meta-analysis to test the hypothesis that rates of TB are different in BCG-vaccinated and BCG-nonvaccinated control populations. In addition to deriving overall efficacy rates for BCG vaccination,[21,22] we also used regression methods to explore sources of variation in protection rates among published studies.

METHODS

Identification of Trials

We sought to identify clinical trials of BCG vaccine efficacy by using a computerized literature search (MEDLINE, using index terms *BCG vaccine*, *tuberculosis*, and *human*), by scanning references of retrieved articles, by reviewing previously compiled lists of BCG studies and review articles on BCG studies, and by contacting experts on BCG vaccination. Members of the study team contacted appropriate individuals at WHO and the Centers for Disease Control and Prevention (CDC) to ensure that all possible studies, published or otherwise, were identified for review. The search was not limited to articles in English, and retrieved studies were translated as needed. Reviewed articles were maintained in a master log, and any reason for exclusion from analysis was documented in the reject log.

Inclusion Criteria

Only studies measuring the efficacy of BCG vaccination in preventing TB cases and/or deaths were included in the meta-analysis. Studies of TB prevalence (such as studies of school children), control programs, and reviews were searched for relevant references, but not included in our analysis. The incidence of TB had been decreasing throughout most of this century even among groups at high risk for TB.[23] Therefore, we only included trials that randomly established concurrent comparison groups receiving and not receiving BCG vaccine, and we required that both groups have equivalent surveillance procedures and similar lengths of follow-up. The available studies of BCG efficacy in health care workers did not meet the inclusion criteria for our analysis. These studies lacked information on the method of allocation of subjects to vaccination[24-26] or lacked appropriate control.[27-33] We excluded studies that evaluated only tuberculin reactions. We reviewed multiple reports of a single trial (when available) to obtain the most complete information possible. However, each included trial contributed only one set of data points for each outcome to the overall meta-analysis of BCG efficacy.

To be included in the analysis, case-control studies had to define the criteria for selecting cases and controls and the method for determining their BCG vaccination status. If controls were identified from a tuberculin-screened population and cases were not, the study was excluded. A total of 1264 titles or abstracts were examined to find studies for possible inclusion. We reviewed 70 studies in detail and identified 26 studies that were included in the analysis.

Data Extraction and Validity Scoring

We attempted to assemble the following information for each study: year of publication, year that vaccination began, study design (including details on randomization), age range of study population, number of patients enrolled, location of study (geographic latitude), strain and dose of BCG used, route of administration, years of follow-up or time since immunization, outcomes measured, and efficacy of vaccine. At least two readers independently extracted the data, with adjudication by a third reader if disagreements occurred.

The reviewed studies had been conducted over a period of more than 60

Table 2.—Case-Control Studies of BCG Vaccine Efficacy and Total Tuberculosis

Source, y	Cases		Controls		Odds Ratio
	BCG	No BCG	BCG	No BCG	
Houston et al,[52] 1990	65	78	148	103	0.58
Miceli et al,[53] 1988	50	125	519	356	0.27
Myint et al,[54] 1987	162	149	977	559	0.62
Sirinavin et al,[58] 1991	57	18	189	18	0.17*
Young and Hershfield,[59] 1986	35	36	163	50	0.39*
Rodrigues et al,[57] 1991	57	54	356	199	0.51*
Packe and Innes,[55] 1988	62	46	336	96	0.36
Putrali et al,[56] 1983	59	44	281	131	0.63
Shapiro et al,[61] 1985	38	140	247	73	0.84*
Patel et al,[60] 1991	57	82	140	156	0.79*
Overall odds ratio (95% confidence interval)					0.50 (0.39-0.64)

*Odds ratio based on matched analysis reported in original study.

years and reflect change in medical practice, reporting techniques, and the design and conduct of studies. We developed scoring systems to assess the potential for bias in study design and ascertainment of diagnosis. For the trials, the scoring system assessed the method of vaccine assignment to the study population, availability for follow-up, equality of surveillance among vaccinated and control arms, criteria used to diagnose TB, and preparation of BCG vaccine. In the case-control studies, we examined potential bias in collecting information (such as vaccine status) on cases and controls, and the criteria used to diagnose TB. We performed all scoring of study design prior to any analysis of results.

Statistical Analysis

Information on vaccine efficacy from the trials and case-control studies was combined separately using random-effects models.[34] We used the DerSimonian and Laird[35] random-effects model to obtain the summary estimates of the log(relative risk [RR]) or log(odds ratio [OR]) from a group of studies. We applied this model separately on stratified subsets of the trials and studies where the outcome (all TB cases, only meningitis, only disseminated TB, or TB deaths), age at vaccination, methods used for the diagnosis of TB (such as laboratory confirmation), or study design (prospective trials and case-control studies) defined the stratification. With respect to study design, the trials were further subdivided in three categories based on their method of allocating subjects to BCG vaccine and control groups: random, alternate, or systematic.

We further developed a random-effects regression model to enable exploration of sources of heterogeneity in the efficacy of BCG vaccine reported in the individual studies. Seven variables potentially associated with BCG efficacy based on literature review and data availability served as covariates to the regression model. We employed seven single-covariate, two two-covariate, and one three-covariate regression models. The random-effects regression model[36] was derived from a method originally proposed by Morris.[37]

We present results from the prospective trials as RRs. In the case-control studies, the OR provides a close approximation to the RR.[38] If BCG vaccination is effective in preventing TB, the observed RR or OR will be less than 1.0. We also present results according to the calculated protective effect, defined as 1 minus the RR (1−RR) or OR (1−OR).

RESULTS

Combining data from the seven trials[15,23,39-43] that used random allocation gave an RR for TB of 0.37 among those vaccinated with BCG (95% CI, 0.18 to 0.74), equivalent to a protective effect of 63% against predominantly pulmonary TB. Adding the two trials[44,45] that used alternate allocation and the four trials[46-49] that used systematic allocation gave an overall RR of 0.49 (95% CI, 0.34 to 0.70) for the 13 trials. The overall protective effect of BCG in preventing TB was 51%.

Seven trials[23,40,42,47,49-51] reported on deaths from TB (including one that only reported on TB deaths). The combined RR for death from TB among participants who had received BCG vaccine was 0.29 (95% CI, 0.16 to 0.53). The BCG vaccination had a 71% protective effect against tuberculous death. Table 1 summarizes for each trial its population size, number of cases and deaths caused by TB, and RRs for cases of TB and for deaths.

Combining data from the case-control studies using the DerSimonian and Laird[35] random-effects model gave results for overall protection by BCG vaccine similar to those provided by the trials. Analysis of the eight studies[52-59] involving populations vaccinated as infants produced a combined OR of 0.45 (95% CI, 0.34 to 0.59), for a protective effect of 55% against TB. Combining 10 case-control studies[52-61] that had 1414 cases of predominately pulmonary TB demonstrated a 50% protective effect for BCG compared with no vaccination. The overall OR for BCG vaccination against TB in these 10 studies was 0.50 (95% CI, 0.39 to 0.64). (Table 2).

Five case-control studies[53,54,57,62,63] conducted in populations vaccinated as infants reported results for cases of tuberculous meningitis (including two that only reported on meningitis). Based on 181 cases of meningitis, BCG vaccination had a protective effect of 64%. The combined OR was 0.36 (95% CI, 0.18 to 0.70). Three studies[53,54,56] reported results on BCG efficacy in preventing disseminated TB, and their combined OR was 0.22 (95% CI, 0.12 to 0.42), demonstrating a 78% protective effect. Three case-control studies[53,58,59] of BCG vaccination during infancy reported data on a total of 108 TB cases confirmed by histologic examination or culture. The combined OR among these cases was 0.17 (95% CI, 0.07 to 0.42), showing a protective effect of 83%.

In a two-covariate, random-effects regression model for exploring variation in BCG efficacy among 13 prospective trials that reported TB cases, geographic latitude and study validity score explained 66% of the between-study variance in the trials.[15,23,39-49] Individually, geographic latitude explained 41% of the variance, and data validity explained 30%. The efficacy of BCG vaccination increased with increasing distance from the equator and with higher study validity. Adding a further variable for mean age at vaccination did not change the results ($P>.50$). Using the variable mean age at vaccination as the only predictor in the random-effects regression model explained only 6% of the variance ($P>.20$). A separate random-effects regression model with the study design covariate (random, alternate, or systematic) as the only predictor explained less than 1% of the variance among the trials. Year of publication explained 4% of the heterogeneity, and year trial began and years of follow-up each explained less than 1%. Among the case-control studies, data validity score was the only variable in a random-effects regression model to explain a substantial amount (36%) of the heterogeneity.

Different strains of BCG were not consistently associated with more favorable or less favorable results in the trials. Different BCG preparations and strains used in the same population gave similar levels of protection.[43,64] The BCG preparations, felt by the investigators to be genetically identical, gave different results in different populations.[65] The most recent case-control studies conducted in the 1980s included many different strains and

found BCG efficacy almost identical to that in the earlier trials.

COMMENT

These analyses of data from 13 prospective trials and separately from 10 case-control studies of BCG efficacy indicate that vaccination with BCG significantly reduces the risk of TB infection by 50% on average. This level of protection persists across a number of subgroups of the studies defined by age at vaccination and study design. More than 85% of the TB cases in the prospective trials were classified by their location or type, with 85% of cases among BCG recipients and controls described as pulmonary TB. Thus, vaccination with BCG was significantly associated with a reduction in pulmonary TB as well as extrapulmonary disease. Higher rates of protection observed against severe forms of TB such as disseminated disease, meningitis, and death may reflect reduced error in the classification of these forms of disease, suggesting that the estimated 50% protection against less severe forms could be artificially low because of higher diagnostic error rates. Among case-control studies, the highest efficacy from BCG vaccination (83% protection) was found in studies reporting cases confirmed by culture or histologic examination. We were unable to quantify the duration of the protective effect of BCG vaccination.

Speculation about reasons for differences in BCG efficacy include the use of different strains of BCG, prevalence of other mycobacterial infections in the study population, genetic or age differences in the study populations, reduced virulence of some *M tuberculosis* strains, and variation in BCG protection against different forms of TB.[15,20,46] Methodological flaws producing biases in the different trials have also been suggested to account for some of the variation in observed efficacy.[66]

Hypotheses for the Madras results and explanations of why the findings may or may not be applicable to other populations have been reviewed.[67] Rather than dwell on a single study, our meta-analysis draws on the broad base of available information, including 10 case-control studies evaluating BCG vaccine efficacy reported since 1980. By using the larger body of data, meta-analysis provides stronger evidence for or against a treatment effect than can be derived from a single study.[68] Meta-analysis also allows the exploration of variation among study results, aiding in the extrapolation of results to other populations.

Regression techniques enabled us to explore the reasons for the heterogeneity among the prospective trials. We found that among seven variables with sufficient data, data validity score and distance of the study site from the equator individually appeared to have the strongest association with BCG efficacy. Jointly, they explained 66% of the between-trial variance. Whether these two variables are surrogates for one or more factors such as quality of follow-up or presence of nontuberculous mycobacteria in the population is difficult to ascertain. Mean age at vaccination and method used for allocation of subjects to vaccine groups did not individually enhance predictiveness for BCG efficacy. Analysis of the case-control studies showed that only the data validity score had any predictive value, explaining 36% of the between-study heterogeneity in BCG efficacy. The demonstration of BCG efficacy across a gamut of study conditions, BCG pedigrees, study populations, age ranges, and vaccine preparations and the 60-year time span suggest that the capacity of BCG vaccination to induce immunity is retained across strains. Further evidence that strain is not very important comes from trials with *Mycobacterium microti* (vole bacillus), which gave protection equal to that of BCG vaccine.[41]

The limitations of this meta-analysis fall into two categories, those attributable to the data available for analysis and those attributable to the techniques generally used to perform the meta-analysis. For example, data reported in the prospective trials were insufficient to analyze the duration of protection afforded by BCG vaccination, and our capacity to assess specific age groups other than infants was limited by the investigators' choices of study populations and lack of age-specific results being reported. We were unable to assess the impact of any single BCG strain or dose because of insufficient data.

Publication bias, or the possibility that unpublished data would contradict the results of published studies, is always a potential source of bias in meta-analysis.[22] We dealt with this potential source of bias in several ways. We contacted experts at the WHO, the CDC, and other organizations to request assistance in identifying any unpublished studies of BCG efficacy. No new studies were found. We also repeated the meta-analysis computations of TB cases from the 13 prospective trials, adding 20 hypothetical trials each equivalent in size to the single largest trial and each showing no benefit from BCG vaccination. The efficacy of BCG in preventing TB remained statistically significant ($P<.01$) even with the inclusion of these hypothetical trials (data not shown).

The analysis including the 20 hypothetical trials was one of several types of sensitivity analyses we performed, with the goal of ascertaining how the results of our meta-analysis would change under various circumstances or different sets of included studies. Our overall conclusions were maintained throughout these sensitivity analyses.

To assess the power of the random-effects regression model to detect the effect of a clinically important covariate on BCG efficacy, 1000 simulated meta-analyses (each containing 10 trials) were generated. Our random-effects regression model maintained good power (92%) for evaluating overall vaccine efficacy (assumed RR, 0.43) when a covariate was included in the model. Because of conservative methods used to compute the 95% CIs, our power (22%) for the covariate was considerably diminished.[36] In other words, the overall estimates of vaccine efficacy are well established, but our ability to detect a significant contribution by a covariate such as age is limited by the small number of BCG vaccine studies available.

The efficacy of BCG is a key element in decisions about use of the vaccine. In making such judgments about use of BCG vaccine in individuals and specific populations, physicians and public health authorities should also consider the incidence, severity, and treatability of TB in the recipient group, side effects of vaccine, potential impact on disease surveillance and detection of new infection, and costs, among other factors. In general, we believe the results of this meta-analysis lend added weight and confidence to arguments favoring use of BCG vaccine.

CONCLUSION

Based on a meta-analysis of data from 14 prospective trials and separately from 12 case-control studies of BCG efficacy, we conclude that BCG vaccination significantly reduces the risk of active TB cases and deaths. The overall protective effect was 50% against TB infections. The BCG vaccine protected against pulmonary TB as well as against disseminated TB (78% protective effect), tuberculous meningitis (64% protective effect), and death (71% protective effect). Age at vaccination was not a significant predictor of BCG efficacy. In a two-covariate model, geographic latitude of the study site and data validity score explain 66% of the between-study variance in the prospective trials.

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