

Bacillus Calmette-Guérin Vaccination and Cancer Prevention: A Critical Review of the Human Experience¹

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Summary

Published studies of the cancer experiences of children vaccinated with *Bacillus Calmette-Guérin* in antituberculosis programs were reviewed and the strengths and weaknesses of each evaluated. There is little evidence that vaccination outside of the neonatal period is effective. If there is an effect of neonatal vaccination, it must convey only a small amount of "protection." Follow-up studies adequate to assess the long-term effects of such vaccination, particularly the risk of lymphoma, have not been done, and recent evidence indicates that such evaluation is warranted.

BCG² was first inoculated into humans in 1921. Since then there have been reports of 7 large controlled clinical trials of the efficacy of BCG in preventing tuberculosis (5, 6, 10, 12, 13, 15, 17). The "protection" against tuberculosis conferred in these trials has ranged from none to 80%. Because of this and other reasons, the field of tuberculosis research has been plagued by a sometimes bitter controversy over the indications for this vaccination. Only in recent years, with the advent of effective chemotherapy for tuberculosis, has the controversy quieted, as the indications for mass vaccination programs have become more restricted. In the last 15 years laboratory evidence has accumulated that BCG vaccination can prevent or suppress challenge from leukemia or tumor grafts in laboratory animals (1). In recent years, 5 analytical and at least 3 descriptive studies have attempted to assess the impact of this vaccination on the risk of cancer, particularly leukemia, in man. The results are just as perplexing and controversial as those concerning tuberculosis.

Studies in Humans

The 1st report to appear was from Canada (8, 9), reporting about a 50% reduction in the risk of leukemia death among children vaccinated neonatally (Table 1).

While not the next chronologically, but certainly philosophically similar to the Canadian study, was a report from Chicago (14) indicating an 85% reduction in the risk of death from leukemia among black children vaccinated neonatally (Table 2). More recently, an expanded analysis con-

firmed this finding and implied a protection of about 80% from death from all tumors (7).

Multiple criticisms have been made of the methods used in both of these studies (16, 18); the major criticisms are 3-fold: (a) matching of death certificates was done only with a roster of vaccinated children. Therefore any failures to "match" because of artifact (migration, name changes, adoption, misspellings) would not only not be credited to the vaccinated group but by "default" would be allocated to the nonvaccinated group; (b) both studies involved the evaluation of service programs, not clinical trials. In the Canadian study the vaccinated were children of parents who volunteered them. While the Chicago study was technically a volunteer study also, the refusal rate among those asked was nil. However, in this instance all of the neonatal vaccination was done at the large county hospital serving the city's indigent population. The appropriateness of using the general population as the comparison group for both of these selected groups is questionable; (c) the analyses did not involve an appropriate denominator in the calculation of a rate in that they failed to utilize the concept of person-years at risk.

Dr. R. Crispen was kind enough to send the Epidemiology Branch all of the vaccination data from Chicago. A reanalysis allowing the calculation of an appropriate denominator reduced the apparent protection from the 1st estimated 80 to 85% for leukemia and all cancers to about 50% for both. Before too much is made of even this 50%, it should be realized that this large reduction in estimate of protection was achieved by accommodating only one of the serious methodological criticisms.

In addition, there have been follow-up reports covering the cancer mortality experience in 3 of the controlled clinical trials of BCG vaccination. In a 21-year follow-up of the Georgia trials (3), no differences were noted between controls and vaccinees in the incidence of leukemia, Hodgkin's disease, or lymphosarcoma (Table 3).

A 15-yr follow-up of the trials in Great Britain (12) reveals a 40% reduction in the risk of death from lymphatic and hematopoietic cancers among the vaccinated but a 60% excess in the risk of death from other malignant neoplasms (Table 4). However, neither of these differences was large enough to achieve statistical significance.

A 19-year follow-up of the largest clinical trial of BCG conducted, that in Puerto Rico, has recently been reported (4). In this study it was possible to ascertain the incidence of cancer, not just the mortality. The average annual incidence rate among the vaccinees was 10.3/100,000 compared to

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² The abbreviation used is: BCG, *Bacillus Calmette-Guérin*.

Table 1

Rate and number of deaths due to leukemia among Quebec children less than age 5 by year of death and BCG vaccination status^a

Year of death	Group			
	Vaccinated		Nonvaccinated	
	No. of deaths	Rate/100,000	No. of deaths	Rate/100,000
1960	8	2.6	22	6.0
1961	13	4.1	29	8.1
1962	16	4.9	30	8.6
1963	9	2.7	22	6.3

^a Adapted from Davignon *et al.* (9).

Table 2

Rate and number of deaths due to leukemia among black children in Chicago, 1964 to 1969, classified by age and BCG vaccination status^a

Age	Group			
	Vaccinated		Nonvaccinated	
	Deaths	Rate/100,000/yr	Deaths	Rate/100,000/yr
<1	0		0	
1-3	0		8	1.9
4-6	1	0.8	13	2.6
Total	1	0.3	21	2.0

^a Adapted from Rosenthal *et al.* (14).

Table 3

Cases of leukemia, Hodgkin's disease, and lymphosarcoma among participants in the Georgia BCG field trials by vaccination group^a

Tuberculin status and vaccination group	Population	Diagnoses		
		Leukemia	Hodgkin's disease	Lymphosarcoma
Vaccinees	16,913	6	4	4
Controls	17,854	6	4	6
Reactors	29,369	20	7	3

^a Adapted from Comstock *et al.* (3).

Table 4

Numbers of deaths and average annual mortality rates (per 100,000) for groups of vaccinated and nonvaccinated teen-agers in England: 15 year follow-up results^a

Trial group	Lymphatic and hematopoietic cancers	Other malignant neoplasms
Vaccinated	2.4 (7) ^b	3.4 (10)
Nonvaccinated (tuberculin negative)	4.1 (8)	2.1 (4)
Vaccinated/nonvaccinated	0.6	1.6

^a Adapted from Medical Research Council (12)

^b Numbers in parentheses, deaths.

that of 7.2/100,000 among the controls. There was a 30% deficit of leukemia among the vaccinees that was not statistically significant. On the other hand, the excess in the total cancer rate among the vaccinees derived from a lymphoma risk which was 8 times that observed among the controls.

The methodological advantages of these 3 clinical trials over the 2 studies based on service programs are 2-fold: (a) randomization of the total group into vaccinated and nonvaccinated optimized the chances for these 2 groups to be comparable to each other; (b) a similar mechanism of ascertainment of cases was utilized for both the vaccinated and the nonvaccinated. The 1 disadvantage is that, while all 3 of these studies involved children of various ages, none involved neonatal vaccination. There has been speculation that maximal protection would be conferred only by vaccination in the neonatal period.

In order to assess more adequately the effect of neonatal vaccination, a descriptive epidemiological approach has been used. In 1971, Kinlen and Pike studied leukemia mortality in portions of Canada and Scotland (11). Looking at overall population statistics they concluded that there was no suggestion that leukemia mortality was lower in Quebec and Glasgow, where BCG is given to a large proportion of the newborn, than in areas without this policy. Tabulations allowing these same kinds of comparisons to be made for nonleukemia cancer deaths have subsequently been prepared by Kinlen (L. J. Kinlen, personal communication to M. Schneiderman of the National Cancer Institute). The conclusions are identical to those reached for leukemia.

Finally, Waaler (19) has presented data from Scandinavia where the "Swedes vaccinated the newborn, the Danes vaccinated school entrants (age 7) and the Norwegians vaccinated school leavers (13-14)." In spite of these marked differences in vaccination practices, the age-specific mortality rates for leukemia in these countries are remarkably similar to each other, the small differences involved being consistent with random fluctuations.

While this is not a risk-benefit analysis, the point needs to be made, since it is often overlooked, that BCG vaccination is not a totally innocuous experience with respect to acute side effects (2). Ulceration and lymphadenitis have been reported to range from 1 to 10%. Recent evidence also indicates that, with newborns, the incidence of osteomyelitis may be as high as 5/100,000.

Conclusions

While the question of whether BCG vaccination protects against human leukemia or other tumors cannot be answered with certainty, several conclusions seem warranted at this time: (a) there is little evidence that such vaccination outside of the neonatal period is effective; (b) if there is an effect of neonatal vaccination, it must convey only a very small amount of "protection;" (c) follow-up studies adequate to assess the long-term effects of such vaccination, including risk of lymphoma, have not been conducted, and recent reports indicate that such evaluation is warranted.

If these points are accepted, then prudence would dictate

that (a) there is certainly no justification for a massive BCG vaccination program as a leukemia prophylaxis; (b) every population group vaccinated in an antituberculosis program that can be studied should be studied (particularly those vaccinated neonatally). The question of a prospective clinical trial of neonatal BCG vaccination as a leukemia prophylaxis is a difficult one, since all the information needed to make such a decision is not known. However, several practical aspects of such a course should be pointed out. If the protection conveyed by BCG vaccination is even as high as 30% in children under age 15 (a generous estimate given all of the data to date), this would involve an average sparing of the death of 1 child/year for every 100,000 vaccinated. In other words, a cohort of 100,000 vaccinated and 100,000 nonvaccinated children would have to be completely followed for 15 years in order just to attain statistical significance at the 5% level (based on 30 observed leukemia deaths *versus* 45 expected by that time). In addition, such a study would have to involve an extraordinarily rigorous scientific design, conduct, and analysis, in order to ensure comparability of the 2 groups. (It would not take a very great difference in social class or prenatal X-ray experience between the 2 groups to produce spuriously an association of this magnitude.) Such a group should then be followed for at least another 10 to 15 years to monitor for any differences in lymphoma risk. In addition, with a sparing effect of 1/100,000, the complications associated with BCG vaccination would have to be quite low to justify such a trial on a risk-benefit basis.

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