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BCG Vaccination and the PPD Test: What the Clinician Needs to Know

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"No reliable method exists for distinguishing tuberculin reactions caused by previous BCG vaccination from those caused by natural mycobacterial infections. Positive tuberculin reactions in BCG-vaccinated persons from high prevalence areas usually indicate infection with *M. tuberculosis*."[1]

INTRODUCTION

The clinician in a migrant health setting faces considerable challenges in the surveillance and control of tuberculosis, some distinct from the issues in a non-migrant setting. BCG (Bacille Calmette Guerin) vaccine is an attenuated vaccine used presently commonly around the world.[2] Since most of the countries from which foreign born farmworkers originate have some form of BCG program,[2] a majority of farmworker patients may potentially have had a BCG vaccination. Thus it is essential that clinicians serving farmworkers have a basic knowledge of BCG and its relation to tuberculosis surveillance.

In their statement on tuberculosis among migrant farmworkers, the Centers for Disease Control recommend that *history of BCG vaccination should be disregarded when interpreting a PPD test.*[1] Other organizations such as the American Thoracic Society have also made this recommendation.[3] However, many health workers who administer and interpret PPD tests believe that a BCG vaccination *always* results in a positive PPD test. Moreover, anecdotal evidence suggests that at times positive PPD's in BCG vaccinated individuals are regarded as *false positives*.

This is a potentially serious breach in the surveillance of tuberculosis in general, but especially among migrant farmworkers. This is because tuberculosis among farmworkers in the USA can be considered an occupational risk, and all farmworkers have a risk for infection far above the non-migrant population. Secondly, foreign born farmworkers originate from countries where TB is 3-60 times more prevalent than in the USA. Thus, a positive PPD in a farmworker is more significant than in almost any other population group.

The proposition that BCG produces a positive PPD would seem an entirely logical one, and this apparent logic is undoubtedly responsible for the persistence of the "BCG = positive PPD" belief. However, the relation between the vaccine and the screening test is rather

complex. This article is intended to explain why a prior BCG vaccination should not influence the interpretation of a PPD test result.

BACKGROUND

The story of how Calmette and Guerin, for whom the vaccine is named, maintained for 14 years the serial cultures necessary for the attenuation and reduction of virulence of *Mycobacterium bovis*, moving the delicate cultures during World War I as the vagaries of the Vichy government and the upsets of war made necessary, is a remarkable but little known one.[4] It is suggestive that the origins of this vaccine are mysterious. Why was a cow tuberculosis chosen? The parent strain, the so called "Lait Nocard," fortuitously secured from a formidable case of cow mastitis, was lost during the war, although the subcultures it produced lead to the strain used in the vaccine today.[5] Indeed, molecular and biochemical study has been unable to trace BCG to a specific strain.[4]

Despite initial fears that BCG would not induce significant or lasting immunity, widespread use began in 1921. However, in the various parts of the world, although the vaccine was produced from cultures of the "Pasteur" strain, there was no standardization at all until 1966.[6]

This historical discursion is intended to convey some of the unique features of this vaccine, and also to indicate that uncertainties about the vaccine have existed since its origination. Much as its origin is mysterious, its history circuitous and its very nature uncertain, the significance of BCG on a clinical and epidemiologic level is anything but straightforward.

ACTION AND EFFICACY OF BCG

The primary protective effect of BCG is to confine a primary tuberculosis infection to the lungs and prevent its hematogenous spread.[7] Thus, the vaccine has greater efficacy against TB meningitis or disseminated TB. Autopsy studies have shown that pulmonary infection is not affected by BCG.[8] The primary protective immunologic action involves the activation of macrophages and subsets of T lymphocytes.[4,9]

The potential for BCG to cause a positive PPD results to some extent from its immunogenicity: its ability to induce a protective immunity. Thus, studies of the efficacy of BCG are relevant. Table 1 shows the results of the classic BCG trials.

Clearly there is great variability in the efficacy of BCG. If a positive PPD is taken as a measure of a successful immunization, as has frequently been done in the past, then on the basis of these studies *a substantial percentage to all of BCG vacinees would be PPD negative.*

Table 1. Major Studies of the Efficacy of BCG*			
Group Vaccinated	**Years of Study**	**N**	**Protective Efficacy**
North American Indians	1935-1938	3,000	80%
Chicago Infants	1937-48	3,381	75%
Georgia Schoolchildren	1947	4,839	zero
Illinois Schoolchildren	1947-48	1,025	zero
Puerto Rican General Pop.	1949-51	77,972	31%
Georgia and Alabama	1950	34,767	14%
Great Britain	1950-52	26,297	78%
South India	1950-55	10,877	31%
* Adapted from Bull Un. Int. Tuberc.;55;1980			

Aside from methodologic issues, there are several explanation for the variability in efficacy, although there is not complete consensus on the relative contributions of each.

A. *Factors affecting all vaccines*
   1. differences in strains used
   2. maintenance of vaccine
   3. administration of vaccine
   4. nutritional status of vaccinees

B. *Factors specific to BCG*
   1. Age when vaccine is given
   2. atypical mycobacteria
   3. prevalence of tuberculosis in region of vaccination
   4. other vaccines (especially flu vaccine[10])

A number of studies have shown that the protective effects (and thus, presumably, likelihood of positive PPD) differs greatly with the age of the vaccinee. BCG is commonly given during the neonatal period. However, some studies have demonstrated that BCG given at the end of the third month provides a higher rate of

response than if given earlier.[11] Moreover, a number of studies have found that immunologic response, measured in terms of antibody levels and PPD reaction, decreases fairly rapidly after vaccination [12-15]. Among Indian (subcontinent) children PPD positivity was 37% one year after vaccination and 27% after five years.[16] Tan found that 42% of six month old infants vaccinated at birth were PPD positive (mean reaction size of 5.89 mm), but only 12% were positive at six years of age (mean size 2.38 mm).[14] Studies of antibody response demonstrate that post-vaccination PPD antibody levels fall over a one year period.[15]

Mycobacteria other than tuberculosis (MOTTs) play an important role in the both the diagnosis and immunization of tuberculosis. MOTTs are agreed to be important in the efficacy of BCG, and they greatly affect the interpretation of the PPD test itself. These often ubiquitous inhabitants of soil and water are typically pathogenic only in the immunocompromised host. In endemic areas the majority of the population has been exposed to MOTTs, and they are cross reactive with PPD.[6] This is the basis for the 10 mm cutpoint of positivity for the PPD test; exposure to MOTTs typically results in a PPD test of 3-8 mm. Uniquely among recall antigen tests, the PPD test is not only expected to demonstrate infection with a pathogenic organism but to differentiate it from "background" exposure to cross reacting environmental non-pathogens.

It is clear from the above that MOTTs contribute substantially to the immunologic context of tuberculosis, and this is also true with regard to the BCG vaccine. A number of researchers contend that MOTTs serve as a kind environmental vaccine, and that exposure to MOTTs confers some protection against tuberculosis. Many contend that this is the reason for much of the variability in the efficacy of BCG.[5,6,17,18] In areas where MOTTs are common, BCG may not confer much additional benefit because the population is already "immunized." Authorities are not unanimous on this subject, but much evidence supports this hypothesis.

There is a fairly good relationship between the prevalence of TB among a population and the degree of protection BCG provides. In general, the greater the prevalence of TB in a region, the greater the efficacy of BCG.[6]

STUDIES OF BCG VACCINATION AND PPD REACTION

It is true that a number of studies have found that BCG vaccinees are more likely to have a positive PPD or a larger PPD than a matched group of non-vacinees, and often these differences are statistically significant.[19-23] However, actual differences in PPD positivity between groups is often not large. Gloyd et al demonstrated PPD positivity in 7.4% of the vaccinated vs 4.5% of the non-vaccinated in Jalisco, Mexico.[21] Godoy found a larger difference: 27.3% PPD positive among the vaccinated and 2.3 of the nonvaccinated.[24] Larsson reports the largest disparity: 49% PPD positive among vaccinated and 3% among nonvaccinees.[22]

The above studies are those which have found the greatest effect of BCG on PPD. However, even those which report the greatest effect do not argue against the CDC recommendation that BCG vaccination be disregarded when interpreting PPD results. This is because in the studies above anywhere from 50%-93% of vaccinees did not convert to a positive PPD. Even if 80% of all vaccinated became PPD positive, if a patient presents with a positive PPD and has been vaccinated, it is impossible to know whether he is in the 80% or the 20%.

Other studies have found less effect on PPD reaction. Mallol found that only 8.8% of 228 Chilean infants vaccinated at birth converted,[25] and another study in Chile found no difference in size of reactions among vaccinated and unvaccinated on initial testing.[26] Kulkarni found only 6% difference in 3000 vaccinated and nonvaccinated Indian children,[27] and 80% of 740 Sri Lankan children with a BCG scar had no response to PPD.[13]

Effect of BCG vaccination in the clinical setting

The studies reviewed above were conducted from a vantage point not usually given the clinician faced with a patient. These researchers were certain of the vaccination status, but the clinician usually cannot be. The farmworker patient may not always be sure, may confuse BCG with other vaccines, and a scar may not always be present.

A number of studies above have documented the absence of a BCG scare even after carefully controlled administration of vaccine. The prevalence of non-scarring in the BCG vaccinate has ranged from 3-16% in these studies.[13,25,26,28,29] This is an issue which has received considerable attention in studies conducted abroad. Sedaghatian found a significant association between the size of the BCG scar and that of the PPD test ($p < 0.001$).[28] In other parts of the world this association has not been seen.[13] In some countries BCG is given 2 or three times, and Sepulveda found that in Chile the number of scars was significantly associated with PPD size.[29]

Turning to studies are more similar to that facing the clinician, in which knowledge of BCG status depends either on the patients self report or the identification of a BCG scar, one finds that there is even less effect of BCG vaccination on PPD status than in the studies above. Joncas found that there was no statistically significant difference in reaction size among BCG vaccinated children and those without GCG. Perez-Stable, in a community based study of Hispanics had similar results. Ciesielski et al, in a random sample of North Carolina migrant farmworkers, also found no significant difference in size of PPD reaction or percent PPD positive between BCG vaccinated Hispanics and Haitians or those without BCG. In fact, the prevalence of positive PPD was higher among those without BCG vaccination.

CONCLUSION

The above has been a review of relevant data on the subject, and demonstrates unequivocally that the *BCG vaccine usually does not cause a positive PPD.* A number of explanations of this imperfect relation between BCG and positive PPD reactions have been discussed. The main factors include:

1. the varying efficacy of the vaccine itself
2. the effects of age.
3. the frequent inability to determine vaccination status

With this as a background to the clinical situation, there are 5 important additional points to consider:

1. Most trials have found that when reactions can be attributed with confidence to BCG the PPD reaction is *less than ten millimeters.*
2. Virtually all individuals are vaccinated in infancy or childhood, and both protective immunity and reactivity to PPD have been extensively documented to decline with age
3. Most patients who may have been vaccinated are adults, in whom whatever effect BCG may have had are greatly diminished.
4. Farmworkers who may have been vaccinated originate from areas of tuberculosis prevalence greatly higher than the United States
5. Farmworkers in general have a risk for tuberculosis far above the non-migrant US population.

Thus, it is clear that all positive PPD's should be regarded as evidence of possible recent infection and evaluated clinically regardless of any history of BCG vaccination or the presence or absence of a BCG scar. This is an essential point for all clinicians to be aware of when screening patients for tuberculosis.

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