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

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The resurgence in tuberculosis necessitates careful surveillance and sensitive detection of cases. The purified protein derivative (PPD) test is the foundation of tuberculosis control. Primary care clinicians are encountering increasing numbers of persons immigrating from countries in which BCG (bacille Calmette-Guérin) vaccination is common. Many health care providers believe that previous BCG vaccination usually results in a positive PPD test, and therefore consider BCG vaccination status when interpreting a positive result on the PPD test.

All articles listed in MEDLINE that included BCG and PPD as key words, a total of 62, were reviewed. Articles published before computerization of the medical literature, a total of 35, were reviewed in *Index Medicus*. This literature review indicates that there is little relationship between BCG vaccination and PPD positivity, and that BCG vaccination status should not be considered in the interpretation of a positive PPD test.

Key words. BCG vaccine; tuberculin test; tuberculosis diagnosis; purified protein derivative test.

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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.

—Advisory Council
Centers for Disease Control

Clinicians whose patient population includes immigrants, refugees, and migrant farmworkers face considerable challenges in the surveillance and control of tuberculosis (TB). Many of the countries these immigrants come from have a high prevalence of TB and some form of the BCG (bacille Calmette-Guérin) vaccination program.[2] Because a majority of these patients may have had a BCG vaccination, it is essential that clinicians serving these populations are knowledgeable about BCG, purified protein derivative (PPD), and tuberculosis infection.

In their statement on tuberculosis among migrant farmworkers, the Centers for Disease Control (CDC) recommend that a history of BCG vaccination be disregarded when interpreting a PPD test.[1] Other organizations, such as the American Thoracic Society, concur.[3]

In spite of the CDC's recommendation, many health care workers who administer and interpret PPD tests believe that a BCG vaccination always results in a positive PPD test. This confusion is understandable, since many authoritative sources have offered erroneous or oversimplified information on this subject that could easily lead to misunderstandings. For example, the text by Mandell[4] on infectious disease states that BCG vaccination results in a positive PPD, implying that such a cause-and-effect relationship exists in every case.

The logical result of this supposition is that a positive PPD in BCG-vaccinated persons should be regarded as a false-positive. An informal survey of 25 attending physicians, residents, and nurses at the author's previous institution found that nearly one half subscribed to some variation of this belief. Such a misconception is a potentially serious breach in the surveillance of tuberculosis in general, but especially among immigrants, refugees, and migrant farmworkers, as most immigrants to the United States originate from countries where TB is 3 to 60 times

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more prevalent than in the United States.[5–7] Research has demonstrated that tuberculosis among farmworkers in the United States can be considered an occupational risk, and that all farmworkers are at a far greater risk for infection than are most other populations.[8] Thus, a positive PPD test in an immigrant or farmworker is more significant than in almost any other population group.

There is some logic to the proposition that BCG produces a positive PPD test result. After all, when a mumps antigen is coadministered with PPD tests as a control antigen to detect anergy, a positive mumps test occurs because of prior mumps vaccination. However, the relation between the BCG vaccine and the PPD test is more complex.

Background

Calmette and Guérin, for whom the BCG vaccination is named, maintained serial cultures for 14 years to attenuate the *Mycobacterium bovis* organism.[9] The parent strain, the so-called *Lait Nocard,* fortuitously secured from a formidable case of cow mastitis, was lost during World War I, although the subcultures it produced led to the strain used in the vaccine today.[10] Widespread use of the BCG vaccine began in 1921; however, there was no effective standardization until 1966.[11]

Action and Efficacy of BCG

The major protective effect of BCG is to confine a primary tuberculosis infection to the lungs and prevent its hematogenous spread through the activation of macrophanges and subsets of T lymphocytes.[9,12,13] Thus, the vaccine affords greater protection against TB meningitis or disseminated TB. Although some autopsy studies have shown that pulmonary infection is not affected by BCG vaccination,[14] other studies have also shown decreased morbidity and mortality from pulmonary tuberculosis among BCG vaccinees as compared with nonvaccinees.[15–19]

Cutaneous reaction to PPD is a type IV delayed hypersensitivity response. It is uncertain to what degree the hypersensitivity response that results in a positive PPD and the immune response that confers resistance to the disease are similar. It is clear that there are differences, as the two are isolable events. Resistance can occur without a positive PPD,[20] and a positive PPD can be produced without conferred resistance to disease.[21]

Such phenomena are probably uncommon. Conversion to positive PPD after BCG vaccination has historically been used as a proxy measurement of immunization.

Table 1. Major Studies of the Efficacy of BCG

Group Vaccinated	Years of Study	Number	Protective Efficacy, %
North American Indians	1935–38	3,008	80
Chicago infants	1937–48	3,381	75
Georgia schoolchildren	1947	4,839	0
Illinois schoolchildren	1947–48	1,025	0
Puerto Rican general population	1949–51	77,972	31
Georgia and Alabama schoolchildren	1950	34,767	14
Great Britain schoolchildren	1950–52	26,297	78
South India schoolchildren	1950–55	10,877	31

Based on data in: Hitze K. Results of the controlled trial on BCG conducted in Chingleput in southern India. Bull Un Int Tuberc 1980; 55:13–4.

Table 1 shows the results of classic BCG trials, in which the great variability in the efficacy of BCG in apparent. If a positive PPD is assumed to indicate the outcome of a successful immunization, then on the basis of these studies, some or all BCG vaccines would be PPD-negative.

Aside from methodologic and technical factors, there are several explanations for the variability in immunization efficacy, although there is no consensus on the relative contributions of each.

Several factors affect all vaccines: differences in strains used, maintenance and administration of the vaccine, nutritional status and age of the vaccinees at the time of vaccination, and the administration of other vaccines (especially for influenza).[22]

A number of studies have shown that the development of immunity and resulting positive PPD varies greatly with the age of the vaccine.[23–26] BCG is commonly given during the neonatal period; however, some studies have demonstrated that BCG given at the end of the third month of life provides a higher rate of response than if given earlier.[23] The immunologic response to BCG, measured in terms of antibody levels and PPD reaction, decreases fairly rapidly after vaccination.[27] Among Indian (subcontinent) children, PPD positivity was 37% 1 year after vaccination and 27% after 5 years.[28] Tan[26] found that 42% of infants vaccinated at birth were PPD-positive (mean reaction size, 5.89 mm), but only 12% were positive at 6 years of age (mean size, 2.38 mm). The reaction sizes at both intervals were substantially less than the positivity cutoff point of 10 mm, as was the case in other studies.[23–26,28]

Mycobacteria other than tuberculosis (MOTTs) play an important role in both the diagnosis of and immunization against tuberculosis. MOTTs affect the efficacy of

BCG, as well as the interpretation of the PPD test. These often-ubiquitous inhabitants of soil and water are typically pathogenic only in the immunocompromised host. In endemic areas, which include the southeastern United States and many tropical areas, the majority of the population have been exposed to MOTTs, which are cross-reactive with *M tuberculosis* on PPD testing.[11] This is the basis for the 10-mm cutoff for positivity of the PPD test, since exposure to MOTTs typically results in a PPD test reaction of 3 to 8 mm.[11] Unique among recall antigen tests, the PPD test is expected not only to demonstrate infection with a pathogenic organism but also to differentiate it from background exposure to cross-reacting environmental nonpathogens.

MOTTs also affect the efficacy of the BCG vaccine. Some researchers contend that MOTTs serve as an environmental vaccine and that exposure to MOTTs confers some protection against tuberculosis. If this theory is true, it would account for much of the variability in the efficacy of BCG.[10,11,29–30] In areas where MOTTs are common, BCG may not confer much additional benefit because the population has already gained some immunity from exposure to MOTTs.

Finally, there is a 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.[11]

Studies of BCG Vaccination and PPD Reaction

Some studies have found that BCG vaccinees are more likely to have a positive PPD or a larger PPD reaction than a matched group of nonvaccinees, sometimes with statistically significant differences.[31–35] For practical purposes, however, the actual difference in PPD positivity between groups is often small. For example, while Gloyd et al[33] demonstrated a statistically significant difference in PPD positivity between vaccinees and nonvaccinees, the difference was only 7.4% vs 4.5%, respectively. Table 2 is a summary of the results of studies that compared PPD reactivity among BCG vaccinees and nonvaccinees. Even in studies such as that of Godoy and colleagues,[36] the great majority of those vaccinated did not convert to a positive PPD. Larsson and co-workers[34] reported the largest disparity: 49% PPD-positive among vaccinated patients and 3% among nonvaccinees.

These studies have found a positive effect of BCG on PPD; however, even those reporting the greatest effect do not argue against the CDC's recommendation that BCG vaccination be disregarded when interpreting PPD results. Fifty percent to 93% of BCG vaccinees do not convert to a positive PPD. Even if 80% of those vaccinated became PPD-positive, it would have little clinical relevance in the interpretation of PPD results. When a clinician is confronted with a patient who presents with a positive PPD and a history of BCG vaccination, it is impossible to determine whether this particular patient is among the majority who converted as a result of the vaccine or the minority who did not.

Table 2. PPD Positivity After BCG Vaccination

Studies	Site of Research	PPD Positivity Post-BCG Vaccination, %
Gloyd et al[33]	Mexico	7.4
Godoy et al[36]	Spain	27.3
Larsson et al.[34]	Sweden	49.0
Mallol et al[37]	Chile	8.8
Kulkarni and Basavaraj[38]	India	6.0
Karalliedde et al[25]	Sri Lanka	20.0
Joncas et al[39]	Canada	23.0
Perez-Stable et al[40]	California	35.0
Ciesielski et al[8]	North Carolina	29.0

PPD denotes purified protein derivative.

Other studies have found less effect on PPD reaction. Mallol and colleagues[37] found that of 228 Chilean infants vaccinated at birth, only 8.8% converted; and another study[41] in Chile found no difference on initial testing in size of reactions between vaccinated and unvaccinated subjects. Kulkarni and Basavaraj[38] found only a 6% difference among 3000 vaccinated and unvaccinated Indian children.

The BCG scar is typically crescentic, measures 2–4 cm, and is located on the left or right deltoid or subacromial area. For those familiar with its appearance, it is a reliable marker for BCG vaccination. However, identification of this scar would indicate little or nothing about the likelihood of a positive PPD. Eighty percent of 74 Sri Lankan children with a BCG scar had no response to PPD.[25] Thus, the presence of BCG scars should not influence clinical management decisions.

Significance of BCG Vaccination in the Clinical Setting

The studies included in this review were conducted with information usually not available in a clinical setting. Although the researchers in these studies were certain of the vaccination status, in most cases, the clinician cannot be certain. The patient may not know his or her BCG status

may confuse BCG with other vaccines, and may not have a BCG scar.

A number of these studies have documented the absence of a BCG scar even after carefully controlled administration of vaccine. The prevalence of nonscarring in the BCG vaccinee has ranged from 3% to 16% in these studies.[25,37,38,41-43] This issue has received considerable attention in studies conducted abroad. Sedaghatian and Shanaa[42] found a significant association between the size of the BCG scar and that of the PPD reaction ($P<.001$). In other parts of the world, this association has not been documented.[25] In some countries, BCG is given two or three times, and Sepulveda and co-workers[43] found that in Chile, the number of scars was significantly associated with PPD reaction size.

In clinical settings, knowledge of BCG status depends either on patient self-report or identification of a BCG scar. Here, too, BCG vaccination has been found to have little influence on PPD status. Joncas and colleagues[39] found no statistically significant difference in PPD reaction size among BCG-vaccinated children as compared with those without BCG. In a community-based study of Hispanics, Perez-Stable and co-workers[40] had similar results. In a random sample of North Carolina migrant farmworkers, Ciesielski and colleagues[8] also found no significant difference in size of PPD reaction or percentage of positive PPDs between BCG-vaccinated and unvaccinated Hispanics and Haitians. In fact, the prevalence of positive PPD was higher among those without BCG vaccination.

Conclusions

BCG vaccine usually does not cause a positive PPD. Regardless of this, it is essential to the surveillance and control of tuberculosis that clinicians consistently disregard any history of BCG vaccination; it serves no useful purpose to even obtain such a history.

The following points summarize the major conclusions that can be drawn from these data: (1) a substantial number and sometimes a majority of BCG-vaccinated persons do not convert to a positive PPD; (2) when reactions can be confidently attributed to BCG, the PPD reaction is usually less than 10 mm; (3) virtually all persons are vaccinated in infancy or childhood, and protective immunity and reactivity to PPD have both been extensively documented to decline with age; and (4) because many immigrants and migrant farmworkers who may have been vaccinated originate from areas where tuberculosis prevalence is much higher than in the United States, positive PPDs should be investigated with a heightened rather than a diminished index of suspicion.

In screening patients for tuberculosis, it is essential that clinicians consider all positive PPDs as evidence of possible primary infection and clinically evaluate patients with positive PPD test results regardless of BCG vaccination history or the presence of a BCG scar.

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