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## How should we manage a patient with a positive PPD and prior BCG vaccination?

### EVIDENCE-BASED ANSWER

Prior bacille Calmette-Guérin (BCG) vaccination increases the likelihood of a positive tuberculosis (TB) 5TU purified protein derivative (PPD) skin test. The PPD response following BCG vaccine varies with age at vaccination, number of years since the BCG vaccination, number of times vaccinated, and number of PPDs performed. An induration of greater than 14 mm is unlikely to be due to prior BCG vaccination (strength of recommendation [SOR]: **A**, based on meta-analysis of validation cohort studies).

The variable reaction after BCG vaccination, along with the desire to detect all

cases of TB, has led to recommendations that all patients with a positive PPD test be treated as true positives. These patients should undergo chest radiography and appropriate treatment, regardless of history of BCG vaccine (SOR: **B**, extrapolation from level 1 study).

A recently developed alternative is the interferon-gamma assay (QuantiFERON-TB Gold test), which may be used in place of, or in addition to, the PPD skin test for patients who are known to have received a BCG vaccine (SOR: **B**, extrapolation from a validation cohort study).

### CLINICAL COMMENTARY

#### Disregard history of BCG immunization when evaluating positive PPDs among immigrants

When I was in residency in Seattle, the experts at the King County TB clinic advised disregarding the history of BCG immunization when evaluating positive PPDs among immigrants. The authors of this review provide evidence confirming this policy. The only new option for helping your patients in weighing the pros and cons of chemoprophylaxis for latent TB is the new

interferon-gamma assay. While 3 times the cost of a PPD, it is a reasonable option for patients who want more specific evidence of latent infection before taking 6 to 9 months of a potentially toxic therapy. I can think of many situations where the specificity of this test may have persuaded some patients to undertake treatment and spared others the risks and inconvenience of isoniazid.

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### Evidence summary

In areas where tuberculosis is prevalent, the World Health Organization recommends BCG vaccination at birth, without

booster doses, to prevent childhood complications of TB infection;<sup>1</sup> however, the vaccine's efficacy is known to be inconsistent. Though BCG vaccine given at birth

can decrease the risk of miliary TB and TB meningitis among children, estimates of its effectiveness in preventing adult pulmonary TB range widely from 0% to 80%.<sup>1</sup>

Though prior BCG vaccination increases the risk of a reactive PPD, this effect is also known to be inconsistent. A 2002 meta-analysis showed that the person's age at the time of their BCG vaccination and the years since vaccination influence the relative risk of a positive PPD (TABLE). The highest relative risk of a positive PPD occurred among patients who received BCG vaccination after infancy and within 15 years of the PPD testing. This same meta-analysis also examined the significance of the size of the PPD response; a subset of 4 studies showed that equal proportions of BCG vaccinated and unvaccinated patients had indurations of 14 mm or more.<sup>2</sup>

BCG vaccine may confound PPD readings, but several studies indicate that PPD can still be a useful screening tool for tuberculosis infection after vaccination. A Brazilian case-control study found that reactions by those BCG recipients later exposed to TB were significantly greater than those with no TB exposure.<sup>3</sup> The study noted that 47.5% of exposed children (defined as those with a household contact) had PPD readings of >10 mm, compared with just 3.6% of control children. In a Quebec cohort of 1198 foreign-born children and young adults, prior BCG vaccination could account for 50% of PPDs with induration of 5 to 9 mm, but only 4% of reactions 10 mm or greater. This study also showed that patients from countries with a high or moderate incidence of TB were more likely to have reactive PPDs than those from countries of low incidence, suggesting that exposure to TB accounts for some of the positive PPDs.<sup>4</sup>

Where it is available, the QuantiFERON-TB Gold test may be used in place of, or in addition to, the PPD for patients who are known to have received a BCG vaccine. This blood test detects interferon-gamma in the serum of people sensitized to

TABLE

### PPD reactions >10 mm when BCG was given during and after infancy

	RECEIVED BCG	NO BCG	RR	(95% CI)
<b>Given in infancy</b>				
Timing of PPD unspecified	22.3%	19.2%	1.16	(1.09–1.23)
PPD less than 15 yrs since BCG	12.6%	5.2%	2.4	(2.00–2.97)
PPD more than 15 yrs since BCG	47.2%	41.0%	1.2	(1.09–1.22)
<b>Given after infancy</b>				
Timing of PPD unspecified	35.6%	17.4%	2.08	(1.89–2.21)
PPD less than 15 yrs since BCG	29.1%	2.9%	10	(5.29–18.99)
PPD more than 15 yrs since BCG	37.6%	47.8%	0.8	(0.74–0.85)

PPD, purified protein derivative; BCG, bacille Calmette-Guérin; RR, relative risk; CI, confidence interval

*Mycobacterium tuberculosis*. Because the test is specific to proteins found in *M tuberculosis*, there is no cross-reactivity with BCG. A Japanese study of 216 BCG-vaccinated individuals showed interferon-gamma assays to be 98.1% specific. The same study reported 89.0% sensitivity for the combination of 2 interferon-gamma assays among 118 TB culture-confirmed individuals.<sup>5</sup> A published report estimated the cost to the health care system per patient tested by a single interferon-gamma release assay as \$33.67, compared with approximately \$11 for PPD testing.<sup>6</sup>

#### Recommendations from others

While the US Preventive Services Task Force (USPSTF) does not make a specific recommendation regarding PPD readings after BCG vaccine, it does recommend screening high-risk populations. The USPSTF further notes that reactions >10 mm should not be attributed to prior BCG vaccine.<sup>7</sup>

#### FAST TRACK

**The interferon-gamma assay, though expensive, has no cross-reactivity with BCG**

The Centers for Disease Control and Prevention (CDC) and American Thoracic Society joint statement recommends against altering guidelines for testing and interpretation among BCG recipients.<sup>8</sup> In 2005, the CDC recommended the QuantiFERON-TB Gold test be used under the same indications as the PPD, noting its potential benefit among those previously immunized with BCG.<sup>9</sup>

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