

The Booster Effect— A Problem for Surveillance of Tuberculosis in Hospital Employees

Hospital employees appear to have a greater chance of acquiring *Mycobacterium tuberculosis* infection than non-hospital workers,¹⁻³ and the greatest threat to both other patients and to hospital employees is the patient or employee with unsuspected disease, who is not handled with appropriate isolation techniques.^{2,3} Because of the dangers of unsuspected tuberculosis in employees, hospitals have been encouraged to set up screening programs to monitor the presence of *M. tuberculosis* infection or disease.^{4,5} It is suggested that the programs begin by providing a tuberculin skin test (purified protein derivative [PPD], 5 tuberculin units) for each employee at the start of the program and for each new employee thereafter. An employee with a positive tuberculin skin test is then evaluated to determine whether there is *M. tuberculosis* infection (positive PPD, no symptoms) or *M. tuberculosis* disease (symptoms and/or signs consistent with tuberculous illness). Those with tuberculosis infection are evaluated for therapy with isoniazid (INH), and either treated or scheduled for chest radiographs at regular intervals if chemotherapy is not warranted.

An employee without *M. tuberculosis* infection (negative PPD) also would be followed at regular intervals; ordinarily this reevaluation consists of repeat PPD skin testing rather than chest radiography. Those who "convert" from negative PPD test to positive PPD reaction when tested next usually are assumed to have developed new infection with *M. tuberculosis*. Usually it is impossible to determine whether the exposure to tuberculosis occurred within or outside the hospital; this often raises significant questions of compensation and liability. In addition, the frequency with which PPD conversion occurs sometimes is used by the hospital to measure the success of attempts to contain the spread of tuberculosis within the hospital.

A number of institutions have now reported their experience with employee tuberculosis screening

programs.⁶⁻¹⁰ These studies report markedly different prevalence of positive PPD skin tests in employees and describe rates of conversion from negative to positive PPD skin tests as high as 8% during the next testing period. However, in one study the rate of conversion was no different between groups with high and low degrees of exposure to patients with tuberculosis,⁷ suggesting that some recent infections with *M. tuberculosis* (as shown by change in skin test reactivity) were not acquired from patients in the hospital, and thus may have been acquired in the non-hospital environment of the employees. In addition, a direct relationship between increasing age and increasing rate of skin test conversion has been noted, suggesting the possibility of boosted PPD skin test reactivity.⁷

Boosting is the phenomenon in which a repeat tuberculin skin test may demonstrate a significantly larger reaction than the initial test in the absence of new infection.¹¹⁻¹⁴ Two factors postulated to be of importance in producing this effect are previous infection with *M. tuberculosis* (for which the skin test reactivity has waned) and/or infection with mycobacteria other than *M. tuberculosis* (producing cross-reaction to PPD-tuberculin). It is postulated, although by no means proven, that the first tuberculin test in a series may stimulate "recall" of sensitivity (in the first case) or enhance cross-reaction (in the second), producing an increased response to subsequent PPD testing.

A study conducted by the Center for Disease Control has examined the impact of the booster phenomenon on tuberculosis screening programs for hospital employees.¹⁴ Consenting employees in 10 hospitals were given a standard tuberculin test using 5 tuberculin units (TU) of Tween-stabilized, bioequivalent PPD tuberculin. Anyone with a tuberculin reaction of less than 14 mm after 48-96 hours was retested with 5 TU of PPD; half of the subjects (chosen at random) had the

second test applied at the time the first test was read, and the other subjects had the second test applied one week after the first test was administered. Participants were given a third test with 5 TU of PPD one year after the first test. Marked increases in reaction size were defined as increases of 6 mm or more, from a reaction of less than 10 mm on the first test to a reaction of 10 mm or more on the second test.

Of the patients who received the second test at the time the first test was read, 1.3% exhibited marked increases; 5.7% of those who received the second test one week after the first test exhibited such increases. Because of the short interval between tests, new infection was not a likely cause of these increases, and control testing minimized reader or dose administration errors as the explanation for these increases (and administration errors may not be as important as once thought¹⁵). Thus, the booster effect appeared to be the most likely cause for the increases. Retesting at one year showed that 13 of the 24 employees whose skin tests had exhibited boosting continued to have a reading of 10 mm or more; none of these employees had evidence of active tuberculous disease.

Similar results were reported in a study by Richards *et al.*,¹⁶ in which 6.6% of volunteers' tuberculin tests converted from negative to positive after one month. None of these converters had evidence of tuberculous disease; 13 of the 14 converters had some reaction to skin test antigens of *Mycobacteria* other than *M. tuberculosis*, compared with reaction to these antigens in 90 of the 199 subjects whose second PPD test remained negative.

Thus, it appears that a second PPD skin test for hospital employees applied one week or more (but less likely 48-96 hours) after a negative initial PPD skin test may be positive up to 6% of the time as a result of a boosting phenomenon related to the skin test, and not because of new infection with *M. tuberculosis*. As a result of these studies, the Center for Disease Control has revised its recommendations for tuberculin testing of new hospital employees.¹⁷ These new guidelines recommend that a new employee receive a PPD skin test at the time of hiring, and that those with reactions of less than 10 mm be given a second test "at least one week and no more than 3 weeks after the first test."¹⁷ The timing of this second test, the strength of tuberculin to be used, and the size of the reaction to be used as an indication of a "conversion" are still in question,^{12,15,18} and are not specified in the CDC publication.

Whether to adopt such a testing program or not still presents a quandary for the acute-care hospital. In favor of such a program are the following points:

1. Some hospital employees who have negative PPD tests at the time of employment and positive tests 6 or 12 months later have "converted" the skin test from negative to positive, but this may be due to the booster phenomenon and not due to new infection with *M. tuberculosis*. If, in fact, the boosting phenomenon was responsible for the change in skin test result, then no liability or

compensation issues should be involved, and use of conversion rate to indicate the frequency of transmission of *M. tuberculosis* in the hospital would provide a falsely elevated estimate. Thus, detection of the boosting effect might be to a hospital's advantage.

2. Whether or not INH is prescribed depends on a number of factors, including how recently infection with *M. tuberculosis* occurred; persons under the age of 35 years ordinarily are considered candidates for INH therapy, and those over the age of 35 whose PPD test has converted within the past year ("recent converters") are considered more likely candidates for therapy than are persons in this age group with a positive PPD test for whom time of infection is not known.¹⁹ Those whose PPD tests have converted as a result of the booster phenomenon are not recently infected and do not need the treatment accorded to a recent converter. The new testing scheme might be useful in identifying these employees.
3. The workload for testing of employees can be reduced to three visits, as positive reactions to PPD tests can be read accurately one week after the test is applied.^{11,12,20,21} Thus, during a second visit one week after the first the original test can be read and the second applied for those with negative first tests.^{12,15} In addition, it should be remembered that these recommendations apply only to the initial testing of new employees, and not to reevaluation tests.

Those who question implementation of the new CDC recommendation make the following points:

1. Increasing attention is being paid to the relatively high costs of adding the second PPD skin test,²² especially in hospitals where risk of acquiring tuberculosis is low,⁶ or logistics of screening are difficult or impossible.²³⁻²⁴ Although PPD screening programs are restricted to new employees, the high turnover of employees in many hospitals makes even initial screening a difficult undertaking.
2. With regard to treatment, the presence of the booster effect is most relevant to personnel 35 years of age or older, in whom chemotherapy might be started only because of evidence of the recent conversion of a PPD test. The decision to offer chemotherapy must be made on the basis of each employee's specific circumstances. If the assessor considers the likelihood that the booster effect accounted for the positive skin test (degree of patient contact, likelihood of exposure to *Mycobacteria* other than *M. tuberculosis*, prevalence of *M. tuberculosis* infection in the patient's home environment, etc.) it is unclear whether the additional step to document the booster effect would affect many therapeutic decisions.
3. Considerations about liability and compensation vary from hospital to hospital. The institution in which development of a tuberculous infection is

likely to have resulted from exposure in the hospital rather than in the community, and in which the employee is likely to seek redress, is one in which it may be worth adding the extra PPD test. However, this situation is by no means universal.

At present, then, the need for all hospitals to implement the new CDC recommendation is far from clear. Additional research may uncover simpler and more practical ways to deal with this problem. Certainly, studies of cost and benefit of implementing the additional PPD test are needed.^{6,7,22} In addition, our knowledge of the booster phenomenon itself is still quite limited.^{12,14,25} We need to know whether those in whom the boosting effect is seen are at increased risk of tuberculous disease, the true time course of the booster phenomenon, the role of *Mycobacteria* other than *M. tuberculosis* in producing this effect,¹⁶ and much more. In the meantime, those of us faced with deciding whether to add this additional step to the program for detection of tuberculosis in employees in our hospitals must continue to base our decisions on "evidence that is not as solidly established as one might wish."¹²

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