## Editorial

# A Test of Tuberculin Quality: Tried and True or Tired and Tattered?

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It is a sad state of affairs when international efforts to control the number-one infectious killer worldwide must rely heavily on a suboptimal diagnostic test developed over 100 years ago and improved upon minimally in the subsequent century. In this month's Journal, Dr. Rangel-Frausto and colleagues add to accumulating evidence reinforcing the pressing need to develop a workable alternative to tuberculin skin testing for the diagnosis of tuberculosis infection.[1]

Robert Koch announced the discovery of tuberculin in 1890.[2] Initially touted as a potential therapeutic agent, it was quickly developed as a diagnostic tool by several methods.[3] The Mantoux intracutaneous test remains in use today.[4] As we enter the new millenium, tuberculin skin testing remains the only practical method for screening populations for asymptomatic infection by tuberculosis. Mantoux skin testing is frequently cited as being only 75% to 90% sensitive for active tuberculosis disease.[2] The long list of potential causes of false-negative skin-test reactions includes a variety of infections (among them, overwhelming tuberculosis), metabolic and nutritional deficiencies, immunosuppressive drugs and immunodeficiency diseases (notably acquired immunodeficiency disease). The specificity of the test is more difficult to estimate but probably is less than 95%, with infection by nontuberculous mycobacteria and vaccination with bacille Calmette-Guérin (BCG) the most common causes of false-positive reactions.[2] Compounded by the vagaries of inconsistent placement and interpretation, differences in quality between batches and brands of product, and the effects of concurrent medical conditions on the sensitivity and specificity of the test, the predictive value of a result in many populations is limited at best.

In this issue of the Journal, Rangel-Frausto and colleagues highlight the importance of having quality product available to maximize the utility of the tuberculin test.[1] They note that the potency of tuberculin supplied from the World Health Organization to Argentina and subsequently prepared and used in Mexico was significantly lower than advertised. The unpredictability of the test is compounded by a system of production, quality control, and administration that may involve numerous different countries and assumes that tests in guinea pigs reliably predict results in humans. There have been several reports of false-positive tuberculin skin tests in the United States as well,[5,6] many of which have been attributed to problems with a particular brand or batch of tuberculin. Even the rigorous US Food and Drug Administration standards do not guarantee uncomplicated use of the product.

Although these authors describe the "low prevalence" of positive tuberculin skin reactions of 26% in their low-risk population, that result would be considered a remarkably high rate in low-risk groups in many countries. While the reasons for the observed rates of skin-test reactions in the low-risk population in Mexico are not elucidated, one potential explanation might be a high rate of past vaccination with BCG. Importantly, the authors demonstrate that a history of BCG vaccination did *not* correlate with a positive tuberculin skin test in their study. This lends further support to the recommendations of the Centers for Disease Control and Prevention[7] and others not to alter one's interpretation of a tuberculin skin test routinely, based on a history of previous BCG vaccination.

For public health personnel, dealing with the common misperception that prior vaccination with BCG precludes any future tuberculin testing is a constant struggle.

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Occupational health services in medical facilities also are familiar with this problem, with healthcare workers often among the most difficult people to convince. National recommendations are available to assist practitioners in educating others about the implications of BCG in the prevention and diagnosis of tuberculosis.[8]

Concern about tuberculin quality is not the only problem with the test. One study found that 64% of physicians, the majority of whom treated patients at high risk for tuberculosis, would incorrectly interpret a skin-test result.[9] Several studies have noted distressingly high rates of variability in the size of reactions of simultaneously applied tuberculins in the same patient and differences in recorded sizes of reactions between experienced readers.[10,11] A free training video, *Tuberculin Skin Testing,* which addresses proper administration and interpretation of the test, is available through the CDC (telephone, 404-639-8135).

Lastly, national expert advisory groups have, from time to time, changed their recommendations for interpretation of tuberculin skin-test results, thereby creating further opportunities for confusion. In recent years, a relatively complicated classification of interpretation has been promulgated, with the threshold for defining a "positive" test dependent on a variety of underlying social or medical risk factors, and the system continues to be modified periodically.[7] As the incidence of tuberculosis in the United States has fallen, the standards for interpretation of results have become more complex. Coinfection with human immunodeficiency virus has arisen as a particularly important consideration affecting the interpretation of test results, as well as decisions about treatment. A useful guide to educational resources on the Internet regarding all aspects of tuberculosis is now available.[12]

Dr. Rangel-Frausto and colleagues join a growing list of investigators heaping evidence upon evidence that the world badly needs a reliable and practical alternative to the current tuberculin skin test.[1] As their article suggests, rather than accepting the current tuberculin skin test as a "tried and true" (and by inference, acceptable) tool, it probably is categorized more appropriately as a tired relic providing suspect results. As talk of eliminating the disease in some countries and enhancing efforts to control it worldwide becomes increasingly earnest,[13] the need for a reliable method of diagnosing tuberculosis infection becomes ever more critical. Investigators are exploring a variety of alternatives, including immunologic assays for serological diagnosis.[14-18] None of these methods, however, appear poised to relegate tuberculin skin testing to obscurity imminently, and we should encourage developmental efforts in any way we can. In the meantime, studies such as this one remain essential to help us make the most of the rusty old tool with which we must work.

## REFERENCES


1. Rangel-Frausto MS, Ponce-de-Leon-Rosales S, Martinez-Abaroa C, Haslv K. Tuberculosis and tuberculin quality: best intentions, misleading results. *Infect Control Hosp Epidemiol* 2001;22:481-484.
2. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. *Clin Infect Dis* 1993;17:968-975.
3. Edwards PQ, Edwards LB. Story of the tuberculin test from an epidemiologic viewpoint. *American Review of Respiratory Diseases* 1960;81:1-47.
4. Mantoux MC. La voie intradermique en tubercalinotherapie. *Presse Med* 1912;20:146-148.
5. Blumberg HM, White N, Parrott P, Gordon W, Hunter M, Ray S. False-positive tuberculin skin test results among health care workers. *JAMA* 2000;283:2793.
6. Sbarbaro JA, Iseman MD. "Koch's lymph" 107 years later—an oldie but not a goldie. *Clin Infect Dis* 1997;25:665.
7. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(RR-6):1-51.
8. Centers for Disease Control and Prevention. The role of BCG vaccine in the prevention and control of tuberculosis in the United States. *MMWR* 1996;45(RR-4):1-19.
9. American Health Consultants. CDC study: physicians know too little about TB. *TB Monitor* January 1994;5-8.
10. Chaparas SD, Vandiviere HM, Melvin I, Koch G, Becker C. Tuberculin test. Variability with the Mantoux procedure. *American Review of Respiratory Diseases* 1985;132:175-177.
11. Bearman JE, Kleinman H, Glyer VV, LaCroix OM. A study of variability in tuberculin test reading. *American Review of Respiratory Diseases* 1964;90:913-919.
12. Kato-Maeda M, Small PM. User's guide to tuberculosis resources on the Internet. *Clin Infect Dis* 2001;32:1580-1588.
13. Institute of Medicine, Committee on the Elimination of Tuberculosis in the United States. *Ending Neglect: The Elimination of Tuberculosis in the United States.* Geiter L, ed. Washington, DC: National Academy Press; 2000.
14. Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. *Lancet* 2000;356:1099-1104.
15. Pottumarthy S, Wells VC, Morris AJ. A comparison of seven tests for serological diagnosis of tuberculosis. *J Clin Microbiol* 2000;38:2227-2231.
16. Pottumarthy S, Morris AJ, Harrison AC, Wells VC. Evaluation of the tuberculin gamma interferon assay; potential to replace the Mantoux skin test. *J Clin Microbiol* 1999;37:3229-3232.
17. Brock I, Munk ME, Kok-Jensen A, Andersen P. Performance of whole blood IFN-gamma test for tuberculosis diagnosis based on PPD or the specific antigens ESAT-6 and CF-10. *Int J Tuberc Lung Dis* 2001;5:462-467.
18. Lalvani A, Pathan AA, McShane H, Wilkinson RJ, Latif M, Conlon CP, et al. Rapid detection of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *Am J Respir Crit Care Med* 2001;163:824-828.