EDITORIAL

Tuberculosis Contacts, Concerns, and Controls: What Matters for Healthcare Workers?

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Healthcare workers (HCWs) are at risk of becoming infected with *Mycobacterium tuberculosis* through occupational exposure. The magnitude of the risk varies according to the setting, occupational group, prevalence of tuberculosis in the community, patient population served, immunocompetency of the worker, and effectiveness of infection control programs.[1,2] HCWs are tested periodically for *M. tuberculosis* infection, and the frequency of testing is determined by the likelihood of exposure to patients with infectious tuberculosis. The QuantiFERON-TB Gold test (QFT-G) is a new tool whose usefulness will greatly benefit from analysis of program-based postmarketing surveillance data.[3]

In 2005, the Centers for Disease Control and Prevention (CDC) published 2 guidelines that highlight the importance of surveillance for tuberculosis infection among HCWs and address the complexities of setting up infection control practices to perform such surveillance.[4,5] Until recently, the only practical method for detecting asymptomatic infection due to *M. tuberculosis* was the tuberculin skin test (TST). The QFT-G is an ex vivo assay that measures the release of interferon-γ (IFN-γ) in whole blood in response to stimulation by antigens that are more specific to *M. tuberculosis* than is tuberculin purified protein derivative (PPD).[6] Because the QFT-G is an ex vivo assay, this test does not cause boosting when it is repeated. In healthcare settings where serial testing is conducted, initial 2-step testing with QFT-G is not recommended. For TST-based serial testing for HCWs, initial 2-step testing is necessary to establish a baseline infection status, to avoid interpreting boosting as a new infection, and to prevent subsequent unnecessary treatment for latent tuberculosis infection (LTBI).[4,7]

The CDC recommendations provide "preliminary" guidance for using the QFT-G without the TST.[5] These recommendations are based on a review of the scientific evidence and clinical practice associated with the use of QFT-G performed by a CDC-convened group of experts. We propose that, if the QFT-G guidelines were evaluated with regard to the CDC grading system for ranking recommendations,[8] then category II B ("Alternative; acceptable to offer. Clinical trials that either are not randomized or were conducted in other populations.") would best describe the strength of the recommendations. The major recommendations of the QFT-G guidelines include the following: (1) QFT-G may be used in all circumstances in which the TST is currently used, including sequential testing surveillance programs for infection control (eg, those involving surveillance of HCWs), (2) negative test results should be interpreted cautiously for certain populations (eg, persons recently exposed to tuberculosis [ie, contacts] or persons who are immunocompromised because of HIV infection), and (3) institutions that elect to use QFT-G should collaborate with laboratories in their jurisdiction to ensure that specimens are properly obtained, handled, and processed before and after their arrival in the laboratory. In many settings, the biggest challenge in performing a QFT-G is getting the blood specimen to a qualified laboratory within 12 hours after it is obtained, so that incubation can be performed while the blood cells are viable. The guidelines do not recommend that all HCW testing be done with the QFT-G. Rather, the guidelines account for the fact that the use of QFT-G to detect LTBI is already under evaluation by some infection control programs, and they help further the effort to obtain practice-based evidence that supports a change in practice. General recommendations for the use of QFT-G in healthcare settings were also included in the 2005 tuberculosis infection control guidelines.[4] These guidelines indicate that a single negative test result is sufficient evidence that the HCW is probably not infected with *M. tuberculosis,* that a person with a positive test result need not be retested for surveillance, and that, when using QFT-G for serial testing, a change from a negative result to a positive result should be considered a case of newly diagnosed infection (ie, conversion).

Incorporating the latest information and implementing the most effective methods for tuberculosis control and prevention should be a high priority in all healthcare facilities. HCWs are a critical population for collecting postmarketing data on IFN-γ release assays (IGRAs), such as QFT-G. According to the US Department of Labor, there are approxi-

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mately 14 million US HCWs, many of whom undergo serial skin testing.[9] HCWs are a diverse, yet accessible population with a wide range of LTBI rates and risks of tuberculosis exposure. A tuberculosis surveillance program for HCWs is costly and time-consuming, but the detection of new infection is necessary for discovering *M. tuberculosis* transmission in the healthcare facility and for preventing occupation-related tuberculosis. Infection control practitioners in healthcare facilities are at an important juncture in deciding the future of employee screening practices for tuberculosis. The 2005 CDC guidelines support the use of QFT-G for screening of HCWs and others undergoing serial evaluation for *M. tuberculosis* infection, stating that QFT-G can usually be used in place of (not in addition to) TST.[4] Other experts consider that the evidence for using only QFT-G for surveillance is still too incomplete to warrant its full implementation and short-term and long-term costs, except as part of collecting postmarketing data.

Programs contemplating a change from the TST to the QFT-G need to consider several questions. First, what data show that QFT-G works for occupational surveillance? The QFT-G has been shown to have sensitivity for detection of culture-confirmed tuberculosis that is comparable to that of the TST; the specificity of the QFT-G for detection of *M. tuberculosis* infection is greater than that of the TST.[5] IGRAs require only one visit to a healthcare facility, and the test result can be available within one day. Many HCWs in the United States were born in countries where the incidence of tuberculosis is high and where bacille Calmette-Guérin (BCG) vaccination is routine. Because a QFT-G result is not influenced by BCG vaccination,[6] HCWs may have increased confidence that the test detects new infection. Detection of IFN-γ is done by enzyme-linked immunosorbent assay (ELISA), which is not subject to interreader variability, making interpretation of ELISA results less subjective than interpretation of TST results. However, errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of QFT-G.

Second, how sensitive is QFT-G for detection of LTBI, given that LTBI and active tuberculosis are immunologically different? The subsequent incidence of active tuberculosis disease among persons with positive and persons with negative results of QFT-G has not yet been determined. The consequences of undiagnosed tuberculosis in a HCW are potentially severe.[10,11] If the QFT-G is sensitive for diagnosing LTBI, positive results should be closely associated with the individual's history of exposure and predictive of the risk of progression to active tuberculosis. As with a positive TST result, recent conversion from a negative to a positive QFT-G result should be highly predictive of subsequent tuberculosis if the LTBI is left untreated. The QFT-G is highly specific for LTBI, and once the sensitivity of the QFT-G for LTBI is well established, resources previously expended on follow-up evaluation and any preventive treatment associated with a positive TST result could be concentrated on the smaller group of people who are QFT-G positive.

Third, are QFT-G results reproducible? how soon do the assay results become positive after exposure and onset of infection? and is QFT-G testing cost-effective? IGRAs must be evaluated longitudinally to determine the frequency of reversion and conversion, determine the optimal definition of conversion, and study the repeatability and long-term reproducibility of these new diagnostic tests. Considering the rapid pace of development of IGRA technology and the anticipated availability of additional IGRA-based tests, the options are likely to increase and the questions to become more complex. Programmatic use of these tests now, with careful data collection and analysis, will help establish the future use of these tests. Because a switch from TSTs to IGRAs will represent a major change in the approach to testing HCWs, the use and acceptability of these new tests among healthcare employees and facilities needs to be assessed. Given the large number of HCWs in the United States, it is also important to evaluate the cost-effectiveness of the different testing methods in healthcare settings. Additional studies to assess performance and economic evaluation and decision analysis of IGRAs in low-resource settings are also warranted.

In this editorial, our aim is to demonstrate what we believe might be the most important guideline of all: to find the best balance as to what infection control professionals are ready to implement for the surveillance of tuberculosis among HCWs at this point, when the most highly supported evidence-based recommendations are not yet available. "One-size-fits-all" guidelines do not fit all situations: the new guidelines are best used as a guide, rather than a directive for setting infection control policy. Confirming or excluding the diagnosis of tuberculosis disease and assessing the probability of LTBI among HCWs still require a combination of epidemiologic, historical, physical, and diagnostic findings that should be considered when interpreting TST results and QFT-G results.[4,5] Public health officials now look to postmarketing surveillance and further research in diverse clinical circumstances to help unravel the complexity of pros and cons and the layered societal circumstances of a public health practice.

In this issue of the journal, several articles address the problem of occupational tuberculosis transmission to healthcare personnel and add to the science-to-practice debate focused on the CDC guidelines and plans for their implementation. Among these are the reports by Friedman et al.[12] and Harada et al.,[13] both of which evaluate the use of IGRAs in healthcare settings, but from significantly different approaches. Friedman and colleagues report results of testing HCWs in the United States with QuantiFERON-TB (QFT, an earlier version of QFT-G), which was known to have problems associated with specificity and is no longer commercially available.[12] Harada and colleagues report excellent specificity with QFT-G, yet there are notable differences between the population they studied—Japanese HCWs—and US HCWs,

including a much higher LTBI rate, exposure to a different TST (Nippon 2.5 TU), and a BCG vaccination rate of almost 100%.[13] These differences complicate the extrapolation of study results to US-based HCWs.

We recommend that infection control practitioners consult with local, state, and regional tuberculosis control programs if they are considering switching from the TST to the QFT-G. With each program implementation of the QFT-G and each new report on the experience associated with its use, a larger and more diverse data set will accumulate. The introduction of QFT-G and the 2005 CDC guidelines[4,5] set benchmarks for infection control practice, but many challenges remain in adapting the guidance to each healthcare setting. We support the search for additional evidence by means of more practice-based tuberculosis infection control and public health practices, because much of the evidence that supports current guidelines has arisen from controlled research that does not always translate well to the realities of healthcare practice.

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