Editorial Commentary

Coming-of-Age of Nucleic Acid Amplification Tests for the Diagnosis of Tuberculosis

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(See the article by Laraque et al. on pages 46–54)

Until recently, a laboratory-based diagnosis of pulmonary tuberculosis (TB) has relied on the use of specimens obtained from the respiratory tract of patients; these specimens were tested by use of both smear microscopy (for visualization of stained acid-fast bacilli [AFB]) and mycobacterial culture. This approach has several limitations that have clinical implications. First, although smear microscopy is rapid, its sensitivity is relatively low (~70% for culture-confirmed pulmonary TB, according to a recent systematic review [1], and lower still in many TB program settings). Moreover, smear microscopy cannot reliably distinguish Mycobacterium tuberculosis from nontuberculous mycobacteria, and therefore its positive predictive value is suboptimal in settings (including those in the United States) in which nontuberculous mycobacteria are commonly isolated from respiratory secretions. Mycobacterial culture is sensitive and, when combined with biochemical or molecular species identification methods, specific for TB. However, the use of culture is technically challenging and slow (i.e., it can take up to 6–8 weeks for M. tuberculosis to grow on culture).

In the mid-1990s, 2 rapid diagnostic tests that use nucleic acid amplification (NAA) for the diagnosis of TB were approved by the US Food and Drug Administration (FDA). The Amplified Mycobacterium tuberculosis Direct (MTD) test (Gen-Probe) and the Amplicor M. tuberculosis test (Roche Diagnostics) were approved for use with respiratory tract specimens that tested positive for AFB on smear. In 1999, an enhanced MTD test was approved for use with respiratory tract specimens that tested negative for AFB on smear. These tests can give results within ~6 h. Early prospective laboratory studies that were designed to determine the performance of the MTD test showed that it had a consistently high specificity (99%–100%) and a more variable but generally high sensitivity (94%–100%) when it was used for testing respiratory tract specimens that tested positive for AFB on smear [2]. A recent meta-analysis found that the MTD test had a sensitivity of 97% (95% confidence interval, 95%–98%) and a specificity of 96% (95% confidence interval, 93%–97%) when it was used for testing respiratory tract specimens that tested positive for AFB on smear [3].

Despite the encouraging study results and their commercial availability, these NAA tests for the diagnosis of TB have not been implemented widely in the United States. A notable exception has been in New York City. In this issue of the journal, Laraque et al. [4] report the results of a retrospective study that relied on routine surveillance data to determine the performance of NAA testing among patients who were evaluated for TB in the New York City area and reported to the New York City Department of Health and Mental Hygiene Bureau of Tuberculosis Control during the period from 2000 through 2004. Several laboratories, including the city and state public health laboratories as well as private laboratories, performed NAA testing, at least 68% of which was done using the MTD test. NAA testing was performed on the respiratory tract specimens of 2418 patients. Among the most important findings was that the sensitivity of NAA testing, using a reference standard of M. tuberculosis subsequently isolated in culture, was 79.1% when it was used for testing respiratory tract specimens that tested negative for AFB on smear. In other words, NAA detected just over three-quarters of the microbiologically confirmed cases of pulmonary TB that were not detected by the other widely available rapid test (i.e.,
smear microscopy). Second, the use of NAA on respiratory tract specimens that tested positive for AFB on smear resulted in positive and negative predictive values of 98.7% and 94.5%, respectively. In other words, for respiratory tract specimens that tested positive for AFB on smear, NAA can reliably (albeit imperfectly) distinguish M. tuberculosis, which has associated public health considerations, from nontuberculous mycobacteria. For respiratory tract specimens, in the context of prospective laboratory studies designed to evaluate the performance of NAA testing, the performance characteristics of NAA testing generally were similar to those reported in other studies.

The study by Laraque et al. [4] is important because it confirms that NAA testing can be implemented successfully in public health and other laboratories that would perform the test as a routine service for evaluation of respiratory tract specimens. Moreover, results from this study by Laraque et al. [4] support the notion that the added value of NAA testing, compared with smear microscopy, likely lies in its enhanced sensitivity when used with respiratory tract specimens that tested negative for AFB on smear and its high positive predictive value when used with respiratory tract specimens that tested positive for AFB on smear. On an individual patient level, this enhanced sensitivity is important for determination of early initiation of appropriate TB treatment and for consequent symptom improvement and reduction in morbidity.

To fully appreciate the potential benefits of NAA testing, however, the public health implications of TB must be considered. Unlike for most other medical conditions, pulmonary TB or even suspicion of pulmonary TB typically sets in motion procedures that are temporarily restrictive to the individual patient (e.g., respiratory isolation), in an effort to prevent transmission, as well as resource intensive (e.g., the initiation of contact investigations to identify and evaluate individuals who may have been exposed to the ill person), to prevent secondary cases of TB. For patients whose respiratory tract specimens tested positive for AFB on smear, the use of NAA testing for prompt mycobacterial classification (e.g., whether M. tuberculosis complex or not) can help health care facilities avoid the unnecessary use of respiratory isolation of or contact investigations for patients whose sputum specimens do not contain M. tuberculosis, and it can confirm the need for treatment and public health measures directed against TB in patients whose sputum specimens do contain M. tuberculosis. The prompt diagnosis of pulmonary TB in patients whose specimens tested negative for AFB on smear is also important for public health, because such patients can be infectious to others [5].

The publication of the study by Laraque et al. [4] in this issue of the journal also corresponds in time to the publication of updated guidelines for the use of NAA testing for the diagnosis of TB by the Centers for Disease Control and Prevention, which now “recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations” [6, p. 7]. Accompanying this recommendation is a revised testing and interpretation algorithm. Practically speaking, NAA testing should become routine for all individuals suspected to have pulmonary TB. It is important to note that NAA testing should be used as an adjunct to (and not a replacement for) mycobacterial culture, which remains a prerequisite for drug susceptibility testing in most US laboratories.

Important questions that were not addressed by Laraque et al. [4] remain unanswered, such as the impact of NAA testing programs on patient outcomes and the cost-effectiveness of NAA testing programs. The cost of NAA testing is relatively high ($47.37 per MTD test in a Maryland laboratory in 2007), but cost savings might be realized by a reduction in respiratory-isolation and contact-investigation costs, costs averted by prevention of M. tuberculosis transmission, and reduced costs associated with nonindicated TB treatment [6–8].

Laraque et al. [4] also reported the results of NAA tests of specimens obtained from body sites other than the respiratory tract. A total of 682 specimens were obtained from body sites other than the respiratory tract were tested, with an overall sensitivity of 89.3% and an overall specificity of 74.5%, using culture as the reference standard. The use of NAA on specimens that tested negative for AFB on smear resulted in a sensitivity of 83.2%. The use of NAA on specimens that tested positive for AFB on smear resulted in a positive predictive value of 95.1%. Of particular interest was the use of NAA on 188 cerebrospinal fluid specimens that resulted in a sensitivity of 84.9%. It is important to note that no NAA tests for TB are currently licensed by the FDA for use with specimens obtained from body sites other than the respiratory tract. Although the results of Laraque et al. [4], who did use non–respiratory tract specimens, are encouraging, they provided insufficient detail with respect to specimen processing and type of NAA test used to make additional conclusions.

Therefore, although initial FDA approval for the use of NAA tests for the diagnosis of TB occurred >1 decade ago, these tests now appear to be coming of age. The study by Laraque et al. [4] shows that NAA tests can be implemented successfully in service-oriented nonstudy laboratories and supports the recent revised recommendations by the Centers for Disease Control and Prevention that NAA testing be performed on at least 1 respiratory tract specimen obtained from a patient suspected of having pulmonary TB.

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References