The Race to Eliminate Tuberculosis

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Tuberculosis is a major cause of morbidity and mortality worldwide, but the number of cases is now lower than ever before, both in the United States and in North Carolina. Although case rates are declining, public health funding for tuberculosis is also declining; it remains to be seen whether tuberculosis will be successfully eliminated or whether it will reemerge in the United States.

Tuberculosis is the model of a disease that can only be successfully controlled through the integration of public health practice and individual health care. The responsible organism, *Mycobacterium tuberculosis*, is an obligate pathogen in humans—that is, it requires a host for growth and reproduction, and it must cause disease in order to be transmitted. It is transmitted from person to person via the respiratory route when an individual with pulmonary disease coughs, speaks, breathes, or sneezes. After transmission, disease occurs in a minority of infected persons, and progression to disease can be prevented with appropriate treatment. In theory, the cycle of transmission and progression to active disease can be broken by appropriately identifying and treating both ill individuals and those with latent infections, which would eventually result in disease elimination.

In the United States, vigorous public health efforts over the past 20 years have been directed toward breaking this cycle. Many states, including North Carolina, have eliminated barriers to appropriate tuberculosis treatment by providing free medications to all infected persons. In addition, local health departments routinely identify and test contacts of persons with infectious tuberculosis, thus identifying newly infected individuals (who have latent infections but are at relatively high risk to progress to active tuberculosis) and offering treatment to prevent future disease. These efforts require significant investment of resources; a large 2006 study estimated that in 2002 alone, between 291,000 and 433,000 persons were started on treatment for latent tuberculosis infection [1]. Investment of these resources seems to be paying off; the authors of the study estimated that 4,000 to 11,000 future cases of active tuberculosis were prevented because of this treatment. In fact, the number of tuberculosis cases reported in the United States in 2012 was at a historic low (9,951 cases; incidence rate, 3.2 cases per 100,000 population), representing the 20th consecutive year of decline [2]. Similarly, North Carolina had the lowest number of cases ever reported in 2012 (211 cases; incidence rate, 2.2 cases per 100,000 population), ranking North Carolina 29th among states in terms of incidence rate and 13th in terms of number of cases (Kitty Herrin, personal communication). In addition, the levels of drug-resistant tuberculosis have remained at relatively low levels. In 2011, the most recent year for which data were available, 127 cases of multidrug-resistant tuberculosis were reported in the United States [2], 2 of which were in North Carolina [3].

Although these statistics are encouraging, it is premature to declare victory in the war on tuberculosis—as has mistakenly been done before, with disastrous consequences. Tuberculosis is still being actively transmitted in North Carolina, particularly among disadvantaged minority populations. This disparity is most clearly seen in children with tuberculosis, many of whom have been recently infected. A study performed a decade ago found that, of children reported to be infected with tuberculosis in North Carolina during the period 1994–2002, 88.3% were nonwhite [4]; information in the North Carolina Electronic Disease Surveillance System database indicates that over the subsequent decade (2003–2012), that percentage remained essentially unchanged at about 89% [5]. Tuberculosis case rates are significantly higher among nonwhite populations than among whites both in North Carolina and in the United States as a whole. In 2012 the case rates among Asians, blacks, and Hispanics in the United States were 25.0, 7.3, and 6.6 times higher than the rate among whites, respectively [2].

Much of this health disparity is driven by the increasing proportion of tuberculosis cases attributable to foreign-born persons (imported tuberculosis). In 2012 a record 63% of all reported tuberculosis cases in the United States among individuals whose national origin was known occurred in persons who were foreign-born [2]. In North Carolina, foreign-born individuals accounted for 46% of all reported cases of tuberculosis [5]. These foreign-born cases usually represent infection in the country of origin, followed by reactivation after immigration to the United States. Given that more than 1 million immigrants enter the United States every

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Treatment of Latent Tuberculosis Infection in North Carolina:
Strategies for Improving Adherence

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Successful treatment of patients with latent tuberculosis infection is an important part of North Carolina's strategy for controlling this disease. Latent tuberculosis infection is defined as the presence of *Mycobacterium tuberculosis*, which might later cause disease, in a patient who currently has no symptoms [1]. By successfully treating persons with latent infection who are most at risk of developing active disease, new cases of tuberculosis can be prevented.

The North Carolina Division of Public Health sets goals for adherence to treatment of latent tuberculosis infection. These goals specify the target completion rates of prescribed treatment for patients in 3 categories: 83% of contacts to sputum acid-fast bacilli (AFB) smear-positive tuberculosis patients who start treatment for newly diagnosed latent tuberculosis infection; 73% of immigrants and refugees with abnormal chest radiographs read overseas as consistent with tuberculosis, and who are diagnosed with latent tuberculosis infection during evaluation in the United States and started on treatment; and 65% of all persons (non-contact) who begin treatment for latent tuberculosis infection [2].

Local health departments are challenged to meet these goals. With the world's population becoming more mobile, increasing numbers of people from countries with high rates of tuberculosis infection immigrate to North Carolina. New residents and visitors from other countries may have different cultural beliefs about health and illness, and many do not speak English. Transportation difficulties and coinfection with human immunodeficiency virus (HIV) and viral hepatitis are other obstacles to treatment adherence.

The traditional treatment of choice for latent tuberculosis infection is isoniazid—also known as isonicotinylhydrazine (INH)—taken daily for 9 months without observation. Given the long treatment course, reliance on self-administration, and occasional side effects, it is not unusual for patients to discontinue their medication without consulting a health care provider. When cultural, language, and transportation barriers are also present, there are even more reasons why treatment adherence may fall short of the desired goals.

How can local health departments improve patient compliance with treatment of latent tuberculosis infection? Strategies that increase treatment adherence include shorter treatment regimens with medications other than isoniazid, efficient utilization of human resources to facilitate directly observed treatment, and changes in the messages given to patients.

During the past year, the Centers for Disease Control and Prevention approved guidelines for new treatment regimens for latent tuberculosis infection, which have been adopted by the North Carolina Division of Public Health. Rifampin, one of the mainstays of antibiotic treatment for active tuberculosis, has been approved for unsupervised daily use to treat latent tuberculosis, which allows for a shorter course of therapy (currently 4 months for adults or 6 months for children). Another approved regimen calls for administration of isoniazid and rifapentine once weekly for 12 weeks, under direct observation by a health care professional [3]. Use of these regimens cuts the length of treatment by more than half and improves the chances that patients will complete treatment.

Efficient use of health care personnel can also increase treatment success. As the number of active cases of tu-

year [6], tuberculosis will never be eliminated in this country as long as the disease remains prevalent in the rest of the world.

Continued investment of resources will clearly be needed to prevent a resurgence of tuberculosis in the United States, but these resources may be in jeopardy. Funding provided by the Centers for Disease Control and Prevention (CDC) to state and local tuberculosis control programs has been reduced every year for the past several years. Many state and local government budgets have faced fiscal pressures that in turn put pressure on public health programs. In addition, some of the key tools of tuberculosis control have been limited in recent years. In the past year alone, shortages of key drugs such as isoniazid, amikacin, and intravenous rifampin have been reported [7, 8]. These shortages have resulted in rationing of therapy and delay in initiating treatment of latent tuberculosis [9]. Furthermore, a shortage of the purified protein derivative (PPD) used for the tuberculin skin test has impaired clinicians' ability to screen exposed persons and identify those who are infected and would benefit from treatment of latent tuberculosis [10]. In the face of these shortages, a cynical observer might comment that tuberculosis statistics will continue to improve simply because we cannot detect the infection, due to the lack of PPD, and that we do not have the drugs to treat the disease if we do detect it.

In addition to resource constraints, tuberculosis control may fall victim to its own success. The decline in tuberculosis incidence translates to a decline in clinician experience with the disease, which may result in failure to recognize tuberculosis when it is encountered. Recent evidence supports a link between low levels of clinician experience with tuberculosis and delayed diagnosis. An examination of US surveillance data led to a 2009 report indicating that the

berculosis continues to decline in North Carolina, health departments are turning their attention to preventing new cases. A retrospective chart review of patients with latent tuberculosis infection who were seen in Mecklenburg County during the period 1996–2003 showed that, among patients with latent infection who were close contacts of a patient with active disease, direct observation of treatment resulted in an additional 30% of patients completing treatment (compared with self-administered treatment) [4]. Outreach nurses sometimes take tuberculosis medications to the homes of patients with active tuberculosis, and there are often others living in the same households who have been exposed and who need treatment for latent tuberculosis infection. The outreach nurse can directly observe treatment of these household members with latent infection at the same time that he or she visits the patient with active disease. Health departments have also engaged health care workers other than health department nurses to facilitate directly observed treatment. To minimize transportation barriers and increase convenience, pharmacists and nurses in physician practices have been utilized to observe patients with active disease as they swallow their medications, and these personnel could also observe treatment of those with latent infections. Some states have also been exploring the use of video technology for "direct" observation, which could increase a health department's capacity to observe treatment of latent tuberculosis infection.

Finally, tuberculosis control staff members in North Carolina have found that how they communicate with patients can make a difference in patient compliance. Because patients with latent tuberculosis infection are by definition asymptomatic, many do not understand the importance of treatment to prevent active disease. Spending a few extra minutes to explain how taking 1 or 2 medications for several months can prevent illness, loss of work time, disability, and even death can usually make an impact on the patient's perspective.

All of these strategies can improve adherence to treatment of latent tuberculosis infection, particularly when they are employed in patients at highest risk: close contacts of patients with active disease, children, and those with HIV infection or another chronic illness. Successful treatment of latent tuberculosis can in turn contribute to the continuing decline in North Carolina's tuberculosis rate. NCMJ

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proportion of tuberculosis patients with advanced pulmonary disease (indicated by positive acid-fast smears with cavitation) steadily increased during the period 1993–2006 [11]. Furthermore, the proportion of tuberculosis patients with advanced disease in a given county was increasingly associated with a lower rate of tuberculosis disease in that county, which is particularly problematic because advanced disease is associated with greater infectiousness, and latent disease may be underreported or undetected. Delayed diagnosis of cases in low-incidence areas where providers and patients are less likely to be familiar with tuberculosis may easily lead to local outbreaks and a resurgence of the disease. Creative strategies, including targeted education of providers and high-risk populations, will be needed to prevent the erosion of previously achieved gains in tuberculosis control.

New technologies may help to facilitate continued progress toward tuberculosis elimination (Table 1). Rapid, sensitive, and specific techniques for diagnosing active tuberculosis are essential to reduce diagnostic delay and to increase the likelihood that appropriate treatment will be initiated in a timely fashion. Such techniques are particularly needed as clinical expertise declines and clinicians become less comfortable initiating empiric antituberculous treatment. Unfortunately, standard rapid diagnostic tests (nucleic acid amplification) are challenging to implement from a quality assurance and cost-effectiveness perspective when the number of tests performed is low. Referral laboratories may process enough specimens to make offering such tests feasible, but the delay inherent in sending specimens to referral laboratories and receiving results reduces some of the benefit of rapid testing.

TABLE 1.
Tests for Detecting *Mycobacterium tuberculosis* Infection

Type of test	Test name(s)	Advantages	Disadvantages
Molecular test for *M. tuberculosis* and rifampin resistance	Cepheid GeneXpert test (Xpert MTB-RIF)	• The test has excellent sensitivity and specificity. • Many laboratories already have the machine required to run the test. • The test requires minimal technician time and expertise. • The test provides simultaneous detection of *M. tuberculosis* and rifampin resistance.	• This assay is currently offered by only a few laboratories.
Tuberculin skin test		• The test is inexpensive to perform. • Providers are familiar with the test. • There are extensive data supporting a relationship between a positive test result and the patient's likelihood of developing active tuberculosis in the future.	• A second visit is required to read the test. • Inter-reader reliability is poor. • There is a potential for false-positive test results due to cross-reactivity with the BCG vaccine and environmental nontuberculous mycobacteria.
Interferon-gamma release assays	(1) QuantiFERON-TB Gold In-Tube test (2) T-SPOT.TB test	• Both tests are commercially available in the United States. • These tests require only a single blood draw to obtain a result. • These tests should have a lower likelihood of false-positive results compared with the tuberculin skin test. • These tests eliminate the need for personnel who are experience in reading tuberculin skin tests.	• These tests are significantly more expensive than the tuberculin skin test. • These tests are associated with significant biological and laboratory variability that may confound interpretation.

Note. BCG, bacille Calmette-Guerin.

The Cepheid GeneXpert test (Xpert MTB-RIF), an automated molecular test for *M. tuberculosis* and resistance to rifampin, may overcome some of these barriers. In international studies in tuberculosis-endemic areas, this test demonstrated excellent sensitivity and specificity [12]. This test is attractive in low-incidence settings where the volume of tests performed in laboratories is low. First, many laboratories already have the (expensive) machine required to run the test, as the same machine is used for other commonly ordered tests—such as rapid detection of methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, and vancomycin-resistant *Enterococcus* species. Second, the test requires minimal technician time and expertise to perform. Third, the test provides simultaneous detection of *M. tuberculosis* and of rifampin resistance; the latter is a good marker for multidrug-resistant tuberculosis, which requires a different therapeutic approach.

A second relatively new technology that may help in domestic tuberculosis control is the interferon-gamma release assay. Two such assays are commercially available in the United States: the QuantiFERON-TB Gold In-Tube test and the T-SPOT.TB test. These assays, which measure an in vitro immune response to *M. tuberculosis*–specific antigens, have several advantages over the tuberculin skin test. First, they require only a single blood draw to obtain a result, compared with the 2 office visits needed to perform and interpret a tuberculin skin test. Second, the antigens used in these tests are not present in either the bacille Calmette-Guérin (BCG) vaccine or in most nontuberculous mycobacteria, which should reduce the likelihood of false-positive results compared with the tuberculin skin test. Third, these assays eliminate the need for personnel who are experienced in reading tuberculin skin tests. However, the interferon-gamma release assays are not a panacea. They are significantly more expensive than the tuberculin skin test, do not discriminate between latent and active tuberculosis (neither does the skin test), and have significant associated biological and laboratory variability that may confound interpretation. The CDC recommends use of these tests instead of the tuberculin skin test [13], but the role of these tests in public health practice and tuberculosis elimination remains to be fully determined.

With carefully targeted provider education, new technologies, and sustained support for public health infrastructure, we will continue to make progress toward tuberculosis elimination. Complacency has the potential to undo the work of many decades, and we must remain focused on the core tasks of diagnosing, treating, and preventing tuberculosis, both in the United States and abroad. In 2011 there were an estimated 8.7 million new cases of active tuberculosis in the world, including nearly half a million cases of multidrug-resistant tuberculosis, and there were 1.4 million deaths from tuberculosis [14]. Eighty percent of new tuberculosis cases occur in just 22 high-incidence countries [14]. Given the number of immigrants who enter the United States every year, as well as the not-insignificant burden of tuberculosis among nonimmigrant visitors, our attention must be broader than the confines of our borders. A provocative cost-effectiveness analysis published in 2005 [15] suggested that investing resources in tuberculosis control abroad would provide a greater reduction in US tuberculosis cases than would investing similar resources to detect and treat latent

tuberculosis infections after immigrants enter the United States. As the saying goes, tuberculosis anywhere is tuberculosis everywhere, and we must remain vigilant if we are to see an end to this scourge. NCM

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