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The Replacement Principle of Tuberculosis
Why Prevention Matters

Tuberculosis incidence has steadily declined in the United States during the last 2 decades. Today, the incidence rate of tuberculosis is 3 cases per 100,000 population (1), which is the lowest it has ever been in the United States. But this statistic hides some of the real significance of the disease. To give rise to this rate, 9,421 people developed tuberculosis last year (2). Many of these cases occurred in marginalized groups of people who do not, or cannot, access proper health care to treat or prevent the disease. Moreover, by the time these new cases started receiving treatment, they had already infected an unknown number of contacts and added to the pool of tuberculosis infection in the United States.

In any population, new cases of tuberculosis arise from one of two sources: They may come from recently infected contacts who do not contain the initial infection, often called progressive primary disease, or from contacts with remote infections, years or decades old, who lose control of the infection long held in check, often called reactivation disease. These dynamics of tuberculosis are important because progressive primary disease is driven by unrecognized cases of tuberculosis and ongoing transmission, whereas reactivation disease is driven by the number of individuals in a population with latent tuberculosis infection.

With these few essentials, one can understand why case detection and treatment is given priority in tuberculosis control (3). This strategy identifies and treats prevalent cases but does not address the people with existing infections who are at risk for reactivation disease. Although the United States maintains a national surveillance program for tuberculosis disease, it does not have a parallel program for surveillance of latent infection, and so must rely on contact investigations and periodic surveys to measure latent infection (4).

In this issue of the *Journal*, a pair of companion papers presents the results of a national survey of tuberculosis infection. Using the NHANES (National Health and Nutrition Examination Survey) 2011–2012, Mancuso and colleagues (pp. 501–509) estimated the prevalence of tuberculosis infection to be 4.4% when measured using the traditional tuberculin skin test, and 4.8% when using QuantiFeron-Gold In-Tube (QFT) as the diagnostic test (5).

Although useful, this summary statistic does not tell the whole story. At this prevalence, more than 13 million individuals in the United States today are infected with *Mycobacterium tuberculosis*, which is even more than a decade ago. Similar to tuberculosis disease, infection is not uniformly distributed. The prevalence of infection is higher in foreign-born residents than in citizens born in the United States, especially among Asians. Finally, the prevalence of infection is greater among individuals born before 1945 and seems to wane in older age.

The companion paper by Ghassemieh and colleagues (pp. 493–500) is the largest comparative analysis of the tuberculin skin test and QFT in a population with low prevalence of disease (6). The authors found that the test agreement was only fair, thereby adding a level of uncertainty to the precision of the survey findings. Further concerns such as a stratified sampling design for a clustered disease, unsampled populations at high risk for tuberculosis, and regional variation in nontuberculous mycobacterial infections all limit the interpretation of their findings.

From epidemic theory, we know that tuberculosis epidemics, or any epidemic in general, are perpetuated when one index case is replaced by one or more cases among contacts during their lifetimes. I call this the Replacement Principle of tuberculosis, first described by Wade Hampton Frost more than a century ago (7). It is a useful principle because it is prescriptive: Only by preventing new cases of disease will we be able to reduce and ultimately extinguish an epidemic or, in other words, eliminate tuberculosis.

We have two strategic options available to us based on the Replacement Principle. First, we can prevent new cases by reducing or interrupting transmission. This may be done through early case detection and treatment in high-risk settings or by the use of environmental controls in clinical settings. Second, we can prevent new cases by reducing the likelihood of disease progression among contacts with latent infection. Diagnosis and treatment of latent tuberculosis infection will achieve this aim.

It is on this last strategy that the companion papers published in this issue shed some light. Because of the high prevalence of latent tuberculosis infection among the foreign-born patients, these communities should receive priority for screening and detection of cases of disease and infection. Because the prevalence in foreign-born individuals is determined by the burden of tuberculosis in the country of origin and the immigration patterns, we should engage in the tuberculosis control of these countries. Detection is only part of the process, however, as cases of disease and infection detected through screening must be appropriately treated.

The role of IFN-γ release assays in population surveys such as this one remains unresolved. It appears that the QFT may indeed be most useful in foreign-born individuals who may have received a bacillus Calmette-Guérin (BCG) vaccine at birth, thereby lowering the false-positive proportion in this group. The notion of using these tests in

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selected populations, given the prior probability of infection or BCG vaccination, is an interesting one that bears further analysis.

This national survey reveals a curious paradox: Despite the steady decline of tuberculosis disease in the United States during the last decade, the prevalence of latent tuberculosis infection has remained unchanged. This paradox is best explained by the immigration of individuals with extant latent tuberculosis infection from countries with a high burden of disease. Progress toward tuberculosis control in the United States will be made by partnering with the health ministries of those countries that contribute to tuberculosis in the United States and by working collaboratively with immigrant populations to screen for infection and disease and treat accordingly. By shrinking the pool of latent infection in the country, we will move closer to the goal of tuberculosis elimination by 2035. ■

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