Identifying Priorities for Testing and Treatment of Latent Tuberculosis Infection in the United States

Leonardo Martinez¹ and Jason R. Andrews²

Division of Infectious Diseases and Geographic Medicine, School of Medicine, Stanford University, Stanford, California, USA

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The United States has made substantial progress in reducing the tuberculosis burden over the past 30 years. From 1990 to 2018, there has been a significant decrease in both the national tuberculosis incidence (10.3 to 2.8 per 100 000 persons) and the absolute number of diagnosed cases (25 701 to 9025) [1]. Although national tuberculosis incidence in the United States in recent years is the lowest ever recorded, reaching tuberculosis elimination, defined as 1 tuberculosis case per 1 million persons, will be much more difficult [2]. Under current tuberculosis control measures, some modeling estimates predict that tuberculosis elimination is unlikely by 2100 [3]. There remain critical knowledge gaps about how to prioritize interventions to continue and sustain progress in reducing incidence of tuberculosis and minimize its burden of disability in the United States.

The core public health approach to tuberculosis control in the United States includes timely diagnosis and treatment of active disease and contact investigations to identify recently exposed individuals

for screening and preventive therapy. Because a substantial fraction of tuberculosis infections are not traceable to specific exposures, targeted testing of individuals at high risk of tuberculosis infection or disease progression is an important strategy to identify individuals for the provision of preventive therapy.

There are 2 principal dimensions to consider. The first is the size of each at-risk population and their contribution to the tuberculosis epidemic. For example, the non-US-born population currently accounts for more than 70% of tuberculosis cases in the United States. An earlier model by Shrestha and colleagues [4] found that providing testing and, among those with a positive test, preventive therapy to half of the non-US-born adult population could substantially reduce tuberculosis incidence in the population. The second dimension includes costs and health benefits at the individual level. Cost-effectiveness is likely to be greater in populations with a higher prevalence of latent tuberculosis, higher risks of disease progression, and greater quality-adjusted life expectancy. Even when these risk groups are small, and their contribution to population-level incidence and transmission is limited, prioritizing these populations for prevention efforts yields the greatest benefits for resources invested. Which risk groups would benefit the most depends on local epidemiology, risks of disease progression, programmatic costs, and health gains expected from preventive therapy.

A critical evaluation of these factors has not been previously performed accounting for modern diagnostics, short-course regimens, and contemporary epidemiological and costing data.

To address these knowledge gaps, in this issue of *Clinical Infectious Diseases* Jo and colleagues [5] extended a previous mathematical model [4, 6], drawing up detailed epidemiologic, treatment effectiveness, and costing data to estimate the cost-effectiveness of targeted testing and treatment for tuberculosis infection in key high-risk populations in the United States: persons who are non-US born, incarcerated, experiencing homelessness, or living with human immunodeficiency virus (HIV) or diabetes. The authors focused their analysis on the 4 US states with the largest burden of tuberculosis—California, Texas, New York, and Florida—and simulated a one-time intervention of full-scale testing of all individuals in these risk groups. Under this model, screening was accompanied by provision of self-administered weekly isoniazid and rifapentine for individuals testing positive for tuberculosis infection but ruling out for active disease. Tuberculosis incidence and quality-adjusted life expectancy, as well as costs, were projected over a 30-year horizon.

The authors found that cost-effectiveness, measured in cost per quality-adjusted life-years (QALYs) gained, was consistently greatest among people living with HIV. For testing and treating persons living with HIV, the cost

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Correspondence: J. R. Andrews, Stanford University School of Medicine, Division of Infectious Diseases and Geographic Medicine, 300 Pasteur Drive, Lane L141, Stanford, CA 94305 (jandr@stanford.edu).

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per QALY gained ranged between \$3000 in Florida to \$11 000 in New York. This finding is consistent with prior studies and is largely due to substantially elevated risk of progression from *Mycobacterium tuberculosis* to disease among persons living with HIV [7, 8].

Testing and providing preventive therapy were moderately cost-effective when targeted to individuals who are non-US-born, incarcerated, or experiencing homelessness. These 3 populations have more than twice the prevalence of latent tuberculosis prevalence as the general population. While disease progression rates were not assumed to be greater in these groups, their increased risk of latent tuberculosis makes case finding more cost-effectiveness due to a lower number needed to test. Overall, Jo and colleagues [5] estimated the cost of testing to account for approximately half of the total costs of the latent tuberculosis and treatment program, such that the cost-effectiveness is, as expected, highly sensitive to the prevalence of latent tuberculosis in each risk group. It is possible that the estimates for cost-effectiveness of testing in congregate populations (those experiencing homelessness and incarceration) are conservative, as the model assumed that they mix homogeneously with the general population; in reality, transmission may be greater in prisons and homeless shelters, such that the benefit of prevention is even greater. Additionally, the model did not account for infrastructure costs related to tuberculosis testing and treatment; many correctional facilities and homeless shelters have systems in place for testing for active and latent tuberculosis, which are critical to preventing outbreaks and can be leveraged for preventive therapy.

The study found that treatment for persons living with diabetes was least cost-effective among the high-risk populations investigated. While the risk of developing active tuberculosis is increased among people living with diabetes and latent tuberculosis infection,

the increased risk of tuberculosis infection is more modest and was therefore not explicitly modeled in this analysis. The number of individuals living with diabetes needed to screen to prevent a case of tuberculosis is therefore considerably higher compared with the other populations. Additionally, people living with diabetes have a higher average age and lower quality-adjusted life expectancy, and may experience less benefit from treatment of latent tuberculosis infection. As a result of these factors, the incremental cost-effectiveness ratios for testing and treatment of people living with diabetes was estimated at more than \$200 000 per QALY gained in all 4 states investigated. Targeted testing and treatment of younger people living with diabetes, those with poor glycemic control [9–11], or with overlapping risk groups (eg, foreign-born, homelessness, incarceration) were not explicitly investigated in this analysis but would likely be much more cost-effective.

A further important contribution of Jo et al is the clear illustration of differences in cost-effectiveness of strategies by state. For example, the cost per QALY gained testing and treating homeless persons was \$511 000 dollars in New York but only \$55 000 dollars in Texas. While, in general, the rank order of cost-effectiveness of testing and treatment by risk group was fairly conserved across the states evaluated, the incremental cost-effectiveness in absolute terms varied substantially. In states with differing costs and tuberculosis epidemiologic profiles, we can expect that priority groups may differ. A state-specific approach may be preferable in the United States given the distinct results seen in this analysis [5].

The results of Jo and colleagues' model were sensitive to costs of interferon- γ release assays, toxicity of regimens, and expected declines in tuberculosis incidence in the absence of testing and preventive therapy. The latter was the single most important driver of variation in

model results, but also among the most difficult to predict, as the US tuberculosis epidemic is intertwined with the global tuberculosis epidemic. Advances in tuberculosis control globally through new tools such as vaccines and improved diagnostics may hasten the decline of tuberculosis in the United States as well. Additionally, the advent of newer short-course regimens that may improve treatment completion and biomarker-based prognostics that may identify individuals at highest risk of progression for targeted therapy would improve the overall cost-effectiveness of preventive therapy [12]. As new tools become available and tuberculosis epidemiology continues to shift, the cost-effectiveness of targeted testing and preventive therapy in various at-risk populations should be periodically reappraised.

Continued progress in tuberculosis control in the United States will require focused efforts to identify and serve at-risk populations in whom the epidemic is increasingly concentrated. As tuberculosis declines, the number needed to test to identify latent tuberculosis cases will continue to rise, leading to diminishing returns on public health investments. Prioritizing these investments therefore requires careful analyses to maximize the impact to individuals and the population. Jo and colleagues' model provides a valuable framework for focusing US tuberculosis-prevention efforts in the coming years.

Notes

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