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## One Half of the Pair: Prioritizing Tuberculosis Transmitters for Early Detection

Although there has been considerable progress in the tools available for reducing global TB morbidity—including improved TB treatment options for multidrug-resistant tuberculosis, the programmatic scale-up of rapid molecular diagnostics, and renewed public health efforts—global TB incidence has decreased only incrementally in the past decade, a result driven in large part by the failure to contain community TB transmission in high-prevalence settings (1). The future of global TB control and continued progress toward elimination will depend substantially on reducing transmission.

In high-TB burden settings, individuals with TB are most often detected passively. Case detection may trigger an array of responses that could include household- or venue-based screening to identify secondary cases or to identify individuals who were recently infected. Although active case finding is efficient and can identify additional individuals with TB or *Mycobacterium tuberculosis* infection, the efficacy and efficiency of approaches in active case finding to reduce community rates of TB in high-burden settings are unclear (2–4). One key hurdle is the magnitude of individuals with undiagnosed TB: nearly 40% of all TB cases or approximately 4 million cases per year (1), resulting in prolonged transmissibility and unchecked transmission. Additionally, even those who are eventually diagnosed are estimated to spend a year or more in an infectious state before diagnosis (5). Although all TB is transmitted, are there individuals who are more likely to transmit TB in the community? If so, should those who are most likely to develop and transmit TB be prioritized for early detection activities?

In this issue of the *Journal*, Trevisi and colleagues (pp. 222–233) report on the identification of social, demographic, and clinical characteristics of individuals involved in TB transmission in a

well-described community setting in Lima, Peru (6). Moreover, they also report on the key profiles of individuals who are more likely to be recipients of *M. tuberculosis*. This population-based study, with a prospective collection of demographic and clinical data, allowed a rich source of data for a descriptive analysis. Nearly 75% or 2,518 of *M. tuberculosis* cultures were available for whole-genome sequencing (WGS). Direct transmission (DT) pairs were identified through WGS with pairs having up to three SNPs and a diagnosis of more than 60 days apart, and the first reported patient with TB assumed to be the transmitter. Among the 3.1 million possible isolate pairs, 1,447 (0.06%) pairs were identified with three SNPs or fewer. In a multivariate analysis, the investigators found that young age (<35 yr), male sex, and smoking were risks for being a transmitter (defined as earlier diagnosed individual within a pair). In addition, a history of imprisonment for either the transmitter or the recipient was a risk for being identified as a pair for direct transmission. If either the transmitter or the recipient had a history of alcohol use, the risk was increased. When evaluating the clinical characteristics using this process for identifying direct transmission pairs, features that are well recognized as promoting transmission, such as cavitary chest X-ray and sputum smear status, were identified as significant risks for transmission, which supported the authors' approach. Although it is reassuring that the study findings largely support many key observations described previously (4, 7, 8), they add further nuance to TB transmission dynamics by disaggregating transmission pairs.

A critical determination in this study was the identification of DT pairs on the basis of the prespecified genetic distance threshold (i.e., SNP threshold). Although the threshold utilized in this study is more stringent than usual, the authors based the cutoff values on *a priori* data from the parent study, in which 93% of within-household DT pairs had a genetic distance less than or equal to three SNPs (9). Although the authors performed sensitivity analyses using varying cutoff values, it would have been helpful to present the analysis aligning with a threshold more commonly used in the field (e.g., 5 or more SNPs, or 12 SNPs) (10).

Although the temporal ordering of case detection determined transmitters and receivers within a DT, directionality was assumed

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but neither established nor inferred using WGS data. Using transmission inference tools to project strain pair ordering could further refine and add statistical support for the classification (11). In addition, transmitter and receiver states are likely dynamic and interchangeable (e.g., a transmitter was also a receiver). Whether the characteristics identified in this cohort are externally valid to other regions, such as in low-incidence or HIV hyperendemic settings, will be important to consider in the future.

The authors rightly point out the many limitations that may influence the findings of the study. The authors identify well-known TB-related attributes that may influence transmission dynamics, lending credence to their study. Determining who transmits more efficiently is complex and is likely shaped by clinical (e.g., cavitation) and pathogen (e.g., strain type) features; time to diagnosis and treatment; and, ultimately, how mobile and connected individuals are with others (12).

Efforts to enhance and target early detection are challenged by fundamental scientific uncertainty about differences in infectivity across different TB disease states (13). Specifically, subclinical TB (i.e., microbiologically detectable *M. tuberculosis* infection without typical TB symptoms) can comprise approximately 50% of all prevalent TB at any given moment and is overlooked by most symptom-based strategies. Modeling studies suggest that subclinical TB may be a major source of transmission (14). Whether attributes that are associated with transmitters, identified in this report, also translate to infectious individuals exhibiting minimal symptoms will be important to assess.

Early detection of individuals with infectious forms of TB has been a central ambition of TB control programs for decades. However, the most effective and efficient ways to find individuals who are most likely to transmit TB have eluded TB control programs, particularly in high-burden settings with limited resources. TB prevalence in Peru, like other high-burden countries, is high for many reasons, including social determinants of health. Current approaches for TB control with passive case detection and contact identification have been inadequate to impact the trajectory of the epidemiology substantially. This study highlights an important role of men, particularly young men, and those with histories of incarceration as groups involved in transmission, consistent with a growing body of literature (8, 15). With a better understanding of the characteristics of who transmits TB and to whom, the approach to TB control in high-burden settings can be more focused on the early detection of TB with a symptom-free screening approach in areas such as prisons and areas with many young men as a start. ■

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Barun Mathema, Ph.D.  
Mailman School of Public Health  
Columbia University  
New York, New York

Joseph Burzynski, M.D., M.P.H.  
Bureau of Tuberculosis Control  
New York City Department of Health and Mental Hygiene  
Queens, New York

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