

It Is Time to Focus on Asymptomatic Tuberculosis

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(See the Major Article by Kendall et al on pages e1035–43.)

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Respiratory exposure to *Mycobacterium tuberculosis* (Mtb) can result in a spectrum of immunological and clinical outcomes. At one extreme is “Mtb resistance,” a proposed state in which the innate immune system kills and clears organisms at the lung’s mucosal surface, staving off infection and eventual disease [1]. At the other extreme is “full-blown” tuberculosis (TB), symptomatic pneumonia that features systemic inflammation, expectoration of sputum that contains live Mtb, and classic signs of lung damage on chest X ray. In between these two extremes is a gradient of states that ranges from latent Mtb infection to subclinical disease. TB control strategies largely focus on identification and treatment of people with full-blown TB disease and provide scant guidance on how to identify and manage the spectrum of more “subtle” disease.

Subclinical TB disease is inherently difficult to identify and research, resulting in key gaps in our understanding

of its features and implications for personal and public health. It may be entirely asymptomatic or may feature very subtle symptoms that are not reported by patients during classic TB symptom screening. It may feature negative or paucibacillary sputum and minimal or atypical radiological changes on chest X ray [2]. Our ability to map this part of the spectrum of TB disease reliably to clinical signs, symptoms, and diagnostic tests is further complicated in endemic settings where Mtb exposures are difficult to pinpoint and may occur repeatedly. Courses of anti-TB therapy and immunosuppressing comorbidities such as human immunodeficiency virus (HIV) and diabetes further complicate attempts to define the clinical and immune correlates of this state. Thus, the field lacks clear definition of the borders between subclinical TB disease and its neighbors on the spectrum of disease.

The prevalence of subclinical and mildly symptomatic TB depends on the case-finding and diagnostic strategies that are used to identify them. In this issue of *Clinical Infectious Diseases*, Kendall et al studied an urban population in Uganda, simultaneously enrolling patients who presented to health facilities with TB and conducting a symptom-agnostic prevalence survey using Xpert Ultra MTB/RIF (rifampin) for all adults who could produce sputum [3]. They found that while 99% of facility-based TB cases endorsed symptoms, 30% of people diagnosed through community-based

testing were completely asymptomatic. Further, by including individuals with the lowest level of detectable Mtb DNA (“trace positive”) on the Xpert Ultra MTB/RIF test [4] in their case definition for prevalent TB, they more than doubled TB prevalence estimates compared with scenarios in which these cases would have been excluded. In a recent meta-analysis of TB prevalence surveys, Frascella et al found asymptomatic TB to be a common state, comprising approximately half of total cases [5]. Notably, most of the surveys were conducted before the Xpert Ultra era and so may have underestimated overall disease prevalence. The presence of detectable Mtb DNA does not equate to presence of live Mtb organisms, and there is some controversy over the interpretation of Xpert trace positive sputum results, especially in asymptomatic people [6]. Ruling out false positives is difficult in the setting of community-based screening when participants, by design, lack signs and symptoms of disease. Interestingly, Kendall et al performed C reactive protein testing on all participants and found that the participants with Xpert “trace positive” sputum had levels of inflammation intermediate to those with clear-cut negative and positive Xpert Ultra results. This intriguing finding suggests that subtle TB cannot be ignored.

The significance of asymptomatic and/or paucibacillary TB to personal health is uncertain, creating a challenge when people in these states are referred

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for clinical care. To guide healthcare workers who negotiate this gray zone, we need a better understanding of the natural history of subclinical TB. Do people proceed along the TB disease spectrum in a linear manner such that even the most subtle TB disease will eventually result in full-blown clinical disease? If so, finding and treating TB at the earliest possible stage would be advantageous to prevent full-blown disease and its increasingly recognized chronic lung disease sequelae [7]. Alternatively, it is possible that in a substantial subset of individuals, subtle TB goes unrecognized and untreated but is “self-resolved” by natural anti-TB immune responses that succeed in shifting the host back down the spectrum of disease into a state of controlled (or resolved) *Mtb* infection. Indeed, literature from the preantibiotic era demonstrates that self-cure was common even in patients with full-blown TB [8]. Recent studies of TB immunity in animal models suggest that low levels of concomitant *Mtb* infection may induce immune responses that protect against progression to symptomatic disease upon subsequent aerosolized *Mtb* infection [9, 10]. It is unknown whether this is relevant in humans and if periodic excursions into the realm of subtle TB may result in more competent long-term TB immunity and protection against full-blown TB disease.

From a public health perspective, the critical question is whether people with asymptomatic TB are able to transmit *Mtb* infection to others. In the study by Kendall et al, concordance between Xpert MTB/RIF trace positivity and *Mtb* culture was strikingly low, leaving unanswered questions about whether asymptomatic people with Xpert trace results may be capable of transmitting *Mtb* to susceptible contacts. This question needs to be addressed with urgency. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown that asymptomatic and minimally symptomatic infection can be critically important in disease transmission and that

distinct public health strategies are required to interrupt asymptomatic transmission [11, 12].

In the absence of prevalence survey research infrastructure, finding people who have asymptomatic TB presents a series of logistical and diagnostic challenges. At least some degree of chest X-ray abnormality is present in the large majority of subclinical TB cases [5], and large-scale chest X-ray surveys are feasible in the era of portable digital X-ray machines and increasingly accurate automated imaging algorithms. Such surveys, however, remain costly, and in the absence of an improved understanding of its radiological features, it is still possible that certain types of subtle TB (such as those with minimal or absent radiological features) will be missed. Chest X rays were not included in the survey by Kendall et al, so the radiographic features of their asymptomatic paucibacillary cases remain a mystery. Kendall et al report impressively high rates of sputum collection and add that, importantly, even samples that had low volume and appeared salivary rather than mucoid yielded a substantial proportion of positive Xpert Ultra MTB/RIF results. Thus, they have demonstrated that with correct coaching, healthcare workers can elicit useful respiratory specimens from asymptomatic individuals. Nonetheless, at the current price, large-scale, community-based screening with Xpert Ultra MTB/RIF remains prohibitively expensive. Additionally, while a community-based study in Vietnam suggests that repeated screening may decrease TB prevalence [13], more data from varied settings are needed to provide guidance about the frequency with which such surveys would need to be conducted to achieve epidemic control. Importantly, whole blood transcriptional signatures have been discovered that correlate with subclinical TB [14]. Development of these and other non-sputum biomarkers represents a potentially promising route toward identifying people with incipient

or subtle TB; however, they need to be simplified and made less expensive to be useful in public health strategies.

It is the time to shine a bright light on asymptomatic TB. It was not so long ago that people living with HIV had to wait until they were ill with “full-blown” AIDS until they were eligible for antiretroviral therapy. We now have clear evidence that such an approach was harmful to individual health and contributed to ongoing transmission that fueled the epidemic. It is possible that we will look back at the era in which we waited to treat TB until patients developed full-blown disease with similar regret. Now is the time to accelerate research into the features, sequelae, and implications of subclinical TB. Because it is currently unclear whether diagnosing and treating asymptomatic and paucibacillary TB has personal and public health benefits, well-designed prospective studies in which people with these conditions and their contacts are carefully monitored for clinical, immunological, and transmission outcomes should be conducted. Translating the resulting insights into optimal guidelines for the diagnosis and management of subclinical TB will require multidisciplinary science that includes clinical, epidemiological, and health systems approaches. We need to raise awareness about asymptomatic TB among healthcare workers, public health decision-makers, scientific funders, and the general public. The global response to coronavirus disease 2019 (COVID-19) has shown that focused and multidisciplinary research by the infectious diseases community can result in head-spinning progress. Now is the time to turn that energy to TB, the world’s long-standing leading cause of infectious death, in all its varied and subtle forms.

Notes

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