airway muscle activity may be less effective in REM sleep. However, hypoglossal nerve stimulators are equally effective during REM and non-REM obstruction (16), although this is not necessarily evidence against their model. Thus, although the findings of Messineo and colleagues are certainly interesting and have potentially identified another mechanism by which obstructive frequency increases in REM sleep, it may be premature to dismiss animal literature explaining preferential dilator muscle hypotonia in REM and their own tonic genioglossus activity reductions in REM sleep as being unimportant. ■

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# Expanding the Tuberculosis Cascade of Care to Treat Undiagnosed and Subclinical Tuberculosis in High-Burden Settings

Globally, more than 25% of all incident cases of tuberculosis (TB) occur in India, which is more TB cases than in any other country in the world (1). In excess of 2.6 million new cases of TB and approximately 500,000 TB-related deaths occurred in India in 2020. Although India has made strides in TB control, progress has been incremental, and acceleration of progress has been limited in part by systemic delays in diagnosis and initiation of TB therapy.

It has long been appreciated that early TB diagnosis and treatment in India are hampered by the vast and unregulated private healthcare sector (2–4). The scale of this sector cannot be overstated, as nearly half of patients with TB in India may initially seek care from private practitioners (2), where diagnosis, treatment, and reporting practices often do not meet national or

international standards and may not be notified to public health programs. Delays in TB diagnosis may have devastating consequences, extending the duration of infectiousness and leading to acquired and transmitted drug resistance, treatment failure, and TB relapse.

In this issue of the *Journal*, Atre and colleagues (pp. 233–241) revisit this well-articulated problem in a critical setting with a reinvigorated focus (5). In this article, the authors performed a case control study of patients with multidrug-resistant TB (MDR-TB) in Western India, with patients without MDR-TB selected as control subjects. Using questionnaire data, in-depth interviews, routinely collected national TB program data, and data derived from the distribution of molecular probes from RT-PCR testing, the study characterized delays to diagnosis and initiation of care and made inferences about MDR-TB transmission in the Pune metropolitan area in Maharashtra, India.

This study has important strengths, including an emphasis on detailing pathways to care, and highlights challenges in the MDR-TB care cascade in India. The care cascade is substantially impacted by an underresourced private sector leading to more hurdles and increased time to appropriate treatment, which has been shown to be a driver of MDR-TB emergence and TB transmission (6). An additional strength of the paper is the use of the frequency of molecular beacons to approximate TB genetic diversity and serve as a proxy for MDR-TB transmission, which is a clever and programmatic approach. Finally, the study's use of mixed methods (in this case, social and molecular epidemiology) is innovative and effective, as mixed methods can quantitatively define challenges and supply critically important qualitative context (5).

Although there are unique strengths to the study, there are important limitations, many of which the authors acknowledge. Delay in diagnosis and treatment initiation associated with prolonged duration of community transmission is a well-described driver of incident MDR-TB, even in India (7). Participants were MDR-TB cases registered with the national TB control program, were contactable by mobile phone, and did not experience early mortality, which is a case definition susceptible to selection bias. Although previous evidence supports the important role of transmission in MDR-TB, the overrepresentation of Probe E reported here should be interpreted with caution. Probe E includes the *rpoB* mutation S531L (S450L in *Mycobacterium tuberculosis* [MTB]), the most common mutation seen globally, including in the Indian subcontinent (8). Regarding the in-depth interviews, it would be useful to know which themes were probed for and which specific barriers and facilitators were experienced by patients with MDR-TB as they attempted to access care. Despite these limitations, the authors make a convincing case for the need to act on key gaps in the TB care cascade in India.

The authors conclude that there is evidence for delayed access to care owing to a lack of access to molecular testing and challenges intrinsic to the private sector in India, which may be important drivers for MDR-TB transmission. To reduce bottlenecks in the TB cascade of care, the authors support expanding the use of GeneXpert MTB/RIF, targeting high-risk subpopulations, further engaging with the private sector, and directly empowering and supporting patients with TB. These are practical recommendations supported by this study and others (2, 3). Unfortunately, the challenges to TB control are even more substantial and start well before the patient's first contact with the healthcare system.

It is recognized that undiagnosed subclinical TB may be far more prevalent than previously thought, and the presence of MTB bacilli cultured in the sputum of asymptomatic individuals raises the possibility of transmission from persons who would not have sought care (9). A population-based TB transmission study using genomic and epidemiologic data concluded that TB transmission occurred before the onset of any TB symptoms, with one-third of all transmission events occurring during the subclinical TB disease phase (10). A recent meta-analysis of TB surveillance studies has identified subclinical TB as comprising up to 50.4% of all active TB cases globally (9). In India, five regional TB surveys reported that 36–55% of all TB detected was subclinical, with a crude median of 43.1%, indicating a likely substantial subclinical TB burden in India (9, 11) that may be confirmed as an ongoing national TB survey is completed (12).

Current diagnostic tools and screening algorithms may be inadequate for subclinical TB. Updated World Health Organization TB screening guidelines that now incorporate radiographic screening may help with TB detection; however, in resource-limited settings, widespread access may be difficult (13). TB exhibits steep gradients of spatial heterogeneity within high-incidence communities (14). Targeted universal TB screening, independent of symptoms, in high-risk groups or spatial foci of TB transmission within endemic settings are examples of expanded case finding strategies that may enhance detection of subclinical TB cases. Primary diagnostic tests available in most TB programs (i.e., chest radiography, microscopy, or Xpert MTB/RIF) in resource-limited settings, including host diagnostic markers, are often limited in detecting subclinical TB (15). The development of new, point-of-care TB diagnostics that include the detection of subclinical TB is an urgent unmet need.

Stealing a page from our colleagues in the HIV field, one of the important public health goals of infectious disease treatment is prevention. If, therefore, one of the aims of TB treatment is prevention of TB transmission, then we will not get to TB treatment as prevention until we get better diagnostics and a better care cascade for all infectious TB, a vision that must include subclinical TB. ■

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