traits with home testing would be an important step to mitigating this obstacle (15). Even then, additional unanticipated burdens to the health system from added complexity in decision-making and care pathways are likely. Ultimately, to reduce the burden of untreated OSA, it will be incumbent on us to integrate personalized strategies in a way that promotes equitable access to high-quality OSA care. ■

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The Reductionist Conundrum of an "Updated" Definition of Extensively Drug-Resistant Tuberculosis

In September 2006, newspapers announced the arrival of "killer strains" of tuberculosis (TB). "Extensively drug-resistant tuberculosis," or "XDR-TB" as it was later known, gained notoriety following a deadly outbreak in rural KwaZulu-Natal, South Africa. Of the 53 people with the disease, 52 perished quickly (1). Most had been living with HIV, had experienced prolonged diagnostic delays and suboptimal therapeutic regimens, and had inadequate psychosocial and socioeconomic support. However, the humans and their illness experience were forgotten as the global public health community focused on one aspect—the drug susceptibility profile of the infecting organisms (2). XDR-TB came to be defined as disease caused by strains of *Mycobacterium tuberculosis* with *in vitro* resistance to isoniazid and rifampin (multidrug-resistant [MDR] TB) and to the fluoroquinolones and injectable agents, the backbone of MDR-TB treatment at the time (3).

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The then-director of the World Health Organization's (WHO) Global TB Program highlighted the complexity of the "multiple errors" that "contributed to the development of XDR disease in South Africa." His editorial further announced "an opportunity to prioritize tuberculosis control and research efforts, energized by the appearance of highly-resistant strains." (4) Reducing the complex illness experience to a short abbreviation was arguably effective for advocacy and fundraising, especially as emerging social media platforms encouraged brevity. Fifteen years later, there has been progress: novel diagnostics, increased treatment, and a growing evidence base for improved regimens (5). Nevertheless, the limits of reductionist labels to effect meaningful change can be observed in the persistent gaps in XDR-TB diagnosis and care. Of the 48 countries with high TB, TB/HIV, and MDR-TB burden, only 12 meet WHO standards for good testing coverage, that is, fluoroquinolone susceptibility test result for at least 80% of people with rifampin-resistant TB (RR-TB) and rifampin susceptibility test result for at least 80% of people with bacteriologically confirmed TB (6). WHO estimates that 465,000 new MDR/RR-TB (resistant to both rifampin and isoniazid or to rifampin and not isoniazid) cases occurred in 2019. According to earlier estimates, approximately 6.2% or 28,830 of these have XDR-TB (7). But only 18.3% of all patients with XDR-TB (47% of those treated) are expected to experience successful treatment outcomes (6). A new strategy, therefore, is necessary to improve detection of and care for this form of TB.

In this issue of the *Journal*, Roelens and colleagues (pp. 713–722) aim to be part of the solution (8). Their work uses a large individual patient data meta-analysis to identify a group of patients with increased risk of unfavorable MDR/RR-TB treatment outcomes. It supports a new definition of XDR-TB, which was unveiled by WHO in early 2021. XDR-TB is now MDR/RR *M. tuberculosis* with additional resistance to two of three drugs or classes currently considered to be most important to MDR/RR-TB treatment: bedaquiline, linezolid, and a fluoroquinolone (moxifloxacin or levofloxacin) (9). Although the definition is resistance based, the analysis examines the association between the absence of drug exposure and treatment outcomes. For example, the analysis poses the following question: if two WHO group A drugs (e.g., bedaquiline and linezolid) are *never* used in the regimen, do more patients experience unfavorable outcomes than if these drugs are *ever* used in the regimen? It finds that odds of unfavorable outcomes were nearly 3 times higher (95% confidence interval, 2.24–3.91) among those who did not receive bedaquiline and linezolid compared with those who did receive these drugs. This finding importantly confirms smaller or single-country studies on the two-drug combination and trial results on bedaquiline (10, 11). The paper then extrapolates that if infecting strains are *resistant* to bedaquiline and linezolid, treatment outcomes will be worse than if the infecting strains are susceptible. Use of absence of exposure as a proxy for resistance is problematic. Mutations that confer resistance may cause other changes to the organism that can enhance or compromise fitness (12). Synergy may occur when drugs are combined; this is theoretically possibly even in strains that are resistant to the drugs used (13). The clinical consequences of these phenomena cannot be assessed when there is no drug exposure. In addition, characterizing exposure as dichotomous (ever vs. never) in an 18- to 24-month, multidrug, dynamic regimen confers substantial risk of bias in effect estimates, which could be avoided by capturing and using full treatment-exposure information and modern epidemiologic methods (14). The authors do acknowledge that use of a proxy for resistance is a limitation. It was necessary because susceptibility testing had been rarely performed for most drugs evaluated in the analysis; fluoroquinolones are the noteworthy exception. The article mentions that next-generation sequencing will inform treatment decisions in the future; its use, however, promises to be unevenly distributed, likely more frequent in lower-TB-burden, higher-income settings.

Optimism about a technological solution belies the larger problem: reducing a complex biological, physiological, and deeply social phenomenon to a label that describes an attribute of the organism. It ignores the historical variability in treatment success: higher if medical therapy is accompanied by psychological, nutritional, and financial support (15). Such terms can also be stigmatizing and traumatizing to individuals with the diagnosis (*see* Figure E1 in the online supplement). And they can be used to restrict access to treatment innovation. For example, pivotal studies of bedaquiline included, and WHO guidance recommended bedaquiline for, patients with a range of forms of DR-TB (10). However, some recommended restricting bedaquiline and linezolid use to pre-XDR or XDR-TB. (16) "Simple" labels stand in stark contrast to the illness reality and to a more holistic, personalized approach to TB, which uses diagnostic and treatment strategies responsive to individual circumstances, characteristics, tolerance, and drug susceptibility profiles (17). The new definition importantly reflects updated tools and evidence on safety and effectiveness of MDR/RR-TB treatment; it affirms that a definition based on injectables is no longer relevant (8). It retains, however, the resistance-based definition that is inadequate to inform the comprehensive interventions necessary to improve care for—and prevent—the illness. ■

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