Eligibility for the Shorter Multidrug-Resistant Tuberculosis Regimen: Ambiguities in the World Health Organization Recommendations

To the Editor:

A shorter regimen for multidrug-resistant tuberculosis (MDR-TB) provides new hope for treatment of this disease. The 9- to 12-month standardized alternative (shorter MDR-TB regimen) to the current 20-month MDR-TB treatment contains kanamycin, moxifloxacin (or gatifloxacin), prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol. It achieved success in 83.7% of patients evaluated in a meta-analysis used to inform new World Health Organization guidelines that recommend the shorter MDR-TB regimen (1). The guidelines, however, leave considerable uncertainty about the eligibility criteria, both their definition and application.

First, considered eligible are "patients with rifampicin-resistant or MDR-TB in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely" (1). Later, the document indicates that "the shorter MDR-TB regimen" should not be used in patients who "have documented or likely resistance to medicines in the regimen" (1). This refinement, however, does not explicitly form part of the recommendation or eligibility criteria.

The uncertainty around this inconsistency affects a large proportion of patients with MDR-TB. As documented in a large meta-analysis, 50% of patients with MDR-TB have isolates resistant to pyrazinamide and 61% to ethambutol (2). Although most rifampicin-resistant strains are resistant to isoniazid, at least at low concentrations, this alone does not constitute a threat to the regimen. The specific isoniazid-resistance–conferring mutation, however, has implications for resistance to other drugs in the shortened regimen: Mutation in *katG* is the most frequent mutation in isoniazid-resistant isolates (66%) and is linked to resistance to high-dose isoniazid; mutations in *inhA* (21%) may also confer resistance to ethionamide (3).

The recommendations suggest that representative drug-susceptibility testing surveillance data may be used to indicate populations of eligible patients. However, they fail to expand to which drugs and at what prevalence of resistance the shorter MDR-TB regimen can be given or should be avoided.

Second, we address the prior exposure criterion: Eligibility is restricted to patients with rifampicin-resistant or MDR-TB "who have not been previously treated with second-line drugs" (1). We note that the vast majority of MDR-TB is due to transmission rather than acquisition (median: 95.9% [95% uncertainty range, 68.0–99.6] of all incident MDR-TB cases) (4). Their disease may be caused by *Mycobacterium tuberculosis* strains that have been exposed to second-line drugs before transmission to the patient. Thus, disease caused by these bacilli may harbor more resistance to other drugs in the regimen. This may be one of the reasons for poorer outcomes in the cohort reported from Uzbekistan (64% of favorable outcomes [5] vs. >80% in settings with less population exposure to second-line drugs), despite the exclusion of patients with resistance to fluoroquinolones or second-line injectables and patients with previous exposure to second-line drugs. Whether the strain has been exposed to second-line drugs is unknowable, so patients with this risk factor will, inevitably, be included under the current guidance.

Rigorous application of the resistance- and exposure-based criteria would require culture-based drug-susceptibility testing. The Hain MTBDR*sl* test, recommended for eligibility screening for the short regimen, is not widely available and has suboptimal sensitivity for fluoroquinolones and second-line injectable drugs (6). Moreover, there is no validated test to rapidly identify resistance to the other drugs.

Although there is tremendous enthusiasm for shorter, more effective MDR-TB treatment, the current World Health Organization guidance on exclusion and practical selection of eligible patients should be refined and clarified. In the absence of such changes, there is considerable risk that, in settings where resistance to other drugs included in the regimen is common among patients with MDR-TB, the shorter regimen will be administered to patients whose profile is very different from those who experienced high proportions of successful treatment in the cohort studies (1) that led to these recommendations. ■

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Limited Benefit of the New Shorter Multidrug-Resistant Tuberculosis Regimen in Europe

To the Editor:

The emergence of multidrug-resistant tuberculosis (MDR-TB), defined as bacillary resistance to at least rifampicin and isoniazid, threatens global TB control. The number of patients notified with MDR-TB worldwide has increased by 261% from 2009 to 2014 (1), and more than one-third of these patients currently live in the European Region of the World Health Organization (WHO) (1).

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Management of patients with MDR-TB is challenging owing to the long duration of therapy required to achieve a relapse-free cure, complex drug regimens, frequent drug-related adverse events, high costs, suboptimal adherence, and overall low cure rates (1, 2).

In the absence of biomarkers to provide guidance for clinicians for individualized durations of MDR-TB therapy (3), WHO recommended, until 2016, that all patients with MDR-TB should receive combination treatment with at least four active drugs for a minimum of 20 months (4).

Results from recent observational studies performed in Bangladesh (5), Cameroon (6), and Niger (7) suggest that shorter-course treatment regimens with a standardized combination of antituberculosis drugs administered for 9 to 12 months would be sufficient to achieve high rates of MDR-TB cure in these settings. After these encouraging results, WHO proposed the use of a standardized short-course MDR-TB regimen with seven drugs (kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol for 4–6 mo, followed by moxifloxacin, clofazimine, pyrazinamide, and ethambutol for 5 mo) for patients with MDR-TB or rifampicin-resistant TB from all regions, regardless of patient age or HIV status (8). Patients are eligible for this regimen when resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, unless there is documented or likely resistance to medicines in the regimen; exposure to any second-line medicines in the shorter MDR-TB regimen for more than 1 month; intolerance to any medicines in the shorter MDR-TB regimen; or risk of toxicity (e.g., drug–drug interactions), pregnancy, extrapulmonary disease, or unavailability of at least one medicine in the shorter regimen (9).

There are concerns that the WHO-recommended shorter regimen might not be effective in all settings (10). As there is a high frequency of *Mycobacterium tuberculosis* strains resistant to second-line antituberculosis drugs in the European region of the WHO (11), we ascertained the proportion of patients who would be eligible for the short-course treatment regimen in Europe by analyzing information from five independent MDR-TB databases that included patients who had comprehensive *M. tuberculosis* drug susceptibility testing (DST) for first- and second-line antituberculosis drugs.

Eligibility for the short-course treatment regimen was evaluated in patients with MDR-TB enrolled consecutively between 2001 and 2016 at three specialized referral centers in Austria (Otto-Wagner-Spital, Vienna), France (Bligny Hospital, Briis-sous-Forges), and Germany (Research Center Borstel, Borstel), from the nationwide Portuguese MDR-TB database, and from the TB Network (TBnet) MDR-TB cohort database, the latter including data from individual patients from 23 European treatment centers in 16 countries. As clofazimine DST is not routinely performed and is restricted mostly to research settings, and the WHO suggests not to consider isoniazid drug resistance, the DST results for the remaining five drugs (kanamycin, moxifloxacin, prothionamide, pyrazinamide, and ethambutol) of the short-course MDR-TB regimen were analyzed. After excluding duplicates, only patients with a full DST, defined as available results for all five