Eligibility for the shorter regimen for multidrug-resistant tuberculosis in Mexico

To the Editor:

We read with interest the articles by Sotgiu *et al.* [1] and Dalcolmo *et al.* [2], which initiated a debate on the suitability of the shorter regimen for multidrug-resistant (MDR) tuberculosis (TB) cases in different settings [2–6]. The shorter World Health Organization (WHO) regimen [7, 8] is composed of an initial phase of 4–6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol.

In summary, TB cases not previously treated with second-line anti-TB drugs are eligible for the shorter regimen (*e.g.* patients previously treated with any of the shorter regimen's drugs and in cases of documented or suspected resistance to one or more of them, with the exception of isoniazid) [7, 8].

The prevalence of resistance to the core drugs comprising the regimen in Europe and Latin America exceeded 60% for the first-line drugs (ethambutol and pyrazinamide), 50% for prothionamide and 40% for the two core drugs (fluoroquinolones and kanamycin) [1–8].

Existing evidence suggests that high-dose isoniazid is effective in the presence of the *inhA* gene (conferring low-level resistance to isoniazid but resistance to ethionamide/prothionamide) and, probably, of the *katG* (conferring intermediate-level resistance to isoniazid) [8]. Only two studies have provided data on genotypic resistance so far [9, 10].

The eligibility to the shorter regimen has not been studied widely in Latin America (with the exception of a single experience in Sao Paulo, Brazil [1]) and in Mexico (one of the largest countries in the region with relatively low drug-resistance prevalence).

As part of a collaborative TB project of the European Respiratory Society and ALAT (Latino-American Society of Thoracic Diseases), the aim of the present study was to assess the suitability to the shorter regimen in Mexico prior to its programmatic implementation, by performing drug susceptibility testing (DST) and genotypic resistance (GenoType MTBDR/MTBDR *plus*; Hain Lifescience, Neheren, Germany) in the Central TB Reference Institute (INER) in Mexico City.

The INER laboratory is validated within the WHO external quality control programme, and DST for first- and second-line drugs is performed by WHO-recommended methods using BACTEC and MGIT 960 (Becton Dickinson, Franklin Lakes, NJ, USA). Cohen's κ statistic was calculated to assess inter-rater agreement between DST and genotypic results. Eligibility was evaluated according to three criteria (table 1): 1) no resistance to fluoroquinolones or injectable drugs, and no *katG* or *inhA* mutations (there is general agreement on this criterion, including WHO and the European Centre for Disease Prevention and Control (ECDC)) [7, 8]; 2) as per criterion 1 plus no resistance to ethambutol (ECDC criterion) [3, 4]; 3) as per criterion 2 but no *katG* mutation (expert opinion only) [9].

Of the 120 cases evaluated, we excluded seven cases with disease caused by *Mycobacterium bovis* strains (three MDR-TB, two rifampicin-resistant (RR)-TB, one RR-TB with additional resistance to fluoroquinolones and one MDR-TB with resistance to second-line injectable drugs); given their intrinsic resistance to pyrazinamide, they are not eligible for the shorter regimen. Out of 112 confirmed consecutive

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TABLE 1 Comparison of the results on phenotypic and genotypic resistance to antituberculosis drugs, Mexico, 2010–2017

	Phenotypic results (n=112)#	Genotypic results (n=57)#	κ (95% CI)
Fluoroquinolone resistant	26/111 (23.4%)	12/57 (21.1%)	0.894 (0.751–1.000)
Ofloxacin resistant	26/111 (23.4%)		
Moxifloxacin resistant	8/49 (16.3%)		
Injectable resistant	13/111 (11.7%)	1/57 (1.8%)	0.226 (-0.145–0.597)
Amikacin resistant	9/111 (8.1%)		
Kanamycin resistant	10/92 (10.9%)		
Capreomycin resistant	6/50 (12.0%)		
Ethambutol resistant	38/112 (33.9%)	19/57 (33.3%)	0.763 (0.585–0.942)
Isoniazid resistant	97/112 (86.6%)	31/57 (54.4%)	0.597 (0.402–0.793)
***katG* and *inhA* mutations**		1/57 (1.8%)	
***katG* mutation only**		18/57 (31.6%)	
***inhA* mutation only**		14/57 (24.6%)	
Pyrazinamide resistant	46/110 (41.8%)		
Eligible for the shorter regimen			
Criterion 1	80 (71.4%)		
Criterion 2	56 (50.0%)		
Criterion 3	50 (44.6%)		

Criterion 1: eligible if no resistance to fluoroquinolones and injectables, and no *katG* or *inhA* mutations; criterion 2: eligible as per criterion 1 plus no resistance to ethambutol; criterion 3: eligible as per criterion 2 but no *katG* mutation (see text for details). #: the denominators vary as not necessarily all 112 strains underwent testing for all the drugs due to lack of reagents.

Mycobacterium tuberculosis MDR-TB cases analysed between 2010 and 2017 (originating from 17 out of 32 Mexican states), 57 underwent genotypic analysis (table 1). Phenotypic resistance to fluoroquinolones was 23.4% (26 out of 111) and genotypic 21.1% (12 out of 57; κ 0.894, 95% CI 0.751–1.000); conversely, there was less resistance to the injectables (11.7% and 1.8%, respectively). Agreement between phenotypic and genotypic tests was good for ethambutol (33.9 *versus* 33.3%, respectively; κ 0.763, 95% CI 0.585–0.942). A single case had combined *katG* and *inhA* mutations, 18 had *katG* only and 14 *inhA* only (table 1).

According to criterion 1, 80 (71.4%) MDR-TB patients would be eligible for the shorter regimen, 56 (50.0%) as per criterion 2 and 50 (44.6%) per criterion 3.

This is the first study comparing phenotypic and genotypic results in Latin America; it will help guide the adoption of the shorter regimen in Mexico. The study has limitations, as the sample size is relatively small and only half of the strains were subject to genotypic tests due to the limited availability of these tests in Mexico (few reference laboratories perform them). It is not easy to explain the low κ value identified for injectables and further evidence is therefore needed. Although the study was performed in a single centre, 85 (75.8%) patients or samples were referred from different states of Mexico with different prevalences of drug resistance.

Our results suggest that, although Mexico has a low prevalence of drug resistance, the shorter regimen cannot be introduced at the programmatic level without adequate testing with rapid methods and DST. Considering 1) the likelihood of drug esistance to ethambutol (most drug-resistant cases in Mexico are failures of a primary regimen including this drug), 2) the excellent DST proficiency results for ethambutol (>90% agreement between the INER laboratory and the supranational laboratory in Mexico City in 2016), and 3) the agreement between phenotypic and genotypic results on this drug, criterion 2 might potentially be the starting point to discuss the national adoption of the shorter regimen in the country.

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