



Resistance profile of drugs composing the “shorter” regimen for multidrug-resistant tuberculosis in Brazil, 2000–2015

To the Editor:

The difficulties in managing multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant (XDR) TB are well known. The regimens are very expensive, often toxic, and require up to 24 months to achieve an acceptable probability of success [1–3].

Based on successful experiences in different settings, the World Health Organization (WHO) recently provided recommendations on the prescription of a new “shorter” regimen to treat MDR-TB, which is also known as the “Bangladesh regimen” [4–8]. The regimen is composed of kanamycin, moxifloxacin (gatifloxacin being the fluoroquinolone originally used in the “Bangladesh” regimen), prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol for an initial period (4–6 months), then moxifloxacin, clofazimine, pyrazinamide and ethambutol for the continuation phase (5 months) [8].

The regimen has interesting characteristics. It is considerably cheaper than the traditional “long” regimen (<USD1000 *versus* >USD20000 or more), has a much shorter duration (9–12 months), and achieves relapse-free success rates exceeding 90% (the positive outcomes of the traditional “longer” regimen are on the order of 50–60%) [8].

The regimen is indicated for patients not previously treated with second-line drugs and unlikely to be resistant to them. WHO recommended the extensive use of rapid molecular testing for the detection of resistances to second-line drugs (Geno Type MTBDRsl) to allow prescription of this regimen to the patients who can benefit from it without risk of developing further drug resistance [8].

Recently, several contributions tried to estimate the proportion of eligible patients in different geographical settings. This ranged from ~10% in Europe to 50% in Pakistan [9–12].

No countrywide information in this sense is available from Latin America. As part of an ongoing collaboration project between the European Respiratory Society (ERS), the Brazilian Society of Respiratory Medicine (SBPT) and the Brazilian National TB Programme, we analysed the information provided by the Brazilian national register (SITE TB), including all patients needing a treatment different from the standard 6 month regimen for (drug-susceptible) TB cases. **Q1**

The aim of this study is to describe the resistance profile of the drugs composing the “shorter” regimen among MDR-TB cases diagnosed between 2000 and 2015.

In Brazil, the MDR-TB regimen is standardised in the majority of cases [13]. Originally, it contained clofazimine and ofloxacin, but in 2006 pyrazinamide replaced clofazimine and in 2010 levofloxacin replaced ofloxacin as the backbone fluoroquinolone (5 months with amikacin or streptomycin (five times a week for 1 month and three times a week for the following 4 months), ethambutol, levofloxacin, pyrazinamide and terizidone, and 12 months with ethambutol, levofloxacin and terizidone).

On this basis we analysed, separately, individuals enrolled between 2000 and 2010 from those treated between 2011 and 2015.

 @ERSpublications

The first nationwide report on the drug resistance profile of the drugs composing the WHO “shorter” regimen in Brazil <http://ow.ly/XfJa3096FsT>

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Absolute frequencies (percentages) and medians (interquartile ranges; IQRs) were used to describe qualitative and quantitative variables. Point and interval (95% CI) estimates were adopted to assess the drug resistance prevalence. Chi-squared or Fisher exact and Mann–Whitney tests were carried out to assess statistically significant differences for qualitative and quantitative variables, when appropriate. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 14 (StataCorp LP 2015; College Station, TX, USA).

Of 6833 patients enrolled, 4477 (66%) were males, with a median (IQR) age of 39 (29–49) years.

The HIV/TB co-infected patients amounted to 7.4% (240/3251) in the period 2000–2010 and 11.7% (369/3156) between 2011 and 2015 ($p < 0.001$). No statistically significant differences were detected between the above-mentioned subgroups in terms of sex. Patients treated between 2011 and 2015 were significantly older (median (IQR) age: 38 (29–48) versus 39 (29–50) years ($p = 0.03$)).

Drug susceptibility testing (DST) was performed using solid media (Lowenstein–Jensen, Middlebrook 7H10/11) until 2010, and then liquid media (Mycobacterial Growth Indicator Tube (MGIT™); BD Diagnostic, Sparks, MD, USA) in quality-assured laboratories.

In Brazil, DST is usually carried out for pyrazinamide and ethambutol. In the period 2000–2010, ethionamide was tested frequently, while in the period 2011–2015 the number of patients tested for this drug was lower, as well as the number of those tested for pyrazinamide. In the first period, fluoroquinolones and injectables were tested in a few patients (100 and 115, respectively), but in the period 2011–2015 DST was performed for these drugs more frequently. DST was not performed for clofazimine.

Overall, a high prevalence of drug resistance was found for pyrazinamide (1474/2950; 50.0%, 95% CI 48.2–51.8%), followed by fluoroquinolones (369/1072; 34.4%, 95% CI 31.6–37.3%), ethambutol (2111/6408; 32.9%, 95% CI 31.8–34.1%), ethionamide (488/1690; 28.9%, 95% CI 26.7–31.0%), kanamycin (112/941; 11.9%, 95% CI 9.8–14.0%) and amikacin (134/1039; 12.9%, 95% CI 10.9–14.9%) (table 1).

Comparing the periods 2000–2010 and 2011–2015, the prevalence of drug resistance decreased for all drugs, with a significant decline for pyrazinamide (51.5% versus 46.7%; $p = 0.01$), ethambutol (37.9% versus 28.3%; $p < 0.0001$) and ethionamide (29.7% versus 19.1%; $p = 0.01$). The prevalence of resistance to fluoroquinolones increased from 30% to 34.9%, without any statistical significance (probably due to increased DST frequency).

The individual DST pattern was somehow heterogeneous during the entire study period (table 1).

Focusing on the drugs composing the “shorter” regimen, in the period 2000–2010, of the 1319 MDR-TB patients undergoing DST for pyrazinamide, ethambutol and ethionamide, 150 (11.4%) were resistant to three drugs. Although the proportion of cases tested was low (table 1), resistance to fluoroquinolones was 30% (largely reflecting the DST for ofloxacin, which was performed on 28 of 100 strains tested for fluoroquinolones), 22.2% for kanamycin and 15.9% for amikacin.

In the period 2011–2015, the prevalence of resistance was 46.7% for pyrazinamide, 28.3% for ethambutol, 34.9% for fluoroquinolones (339/972, again largely reflecting the DST for ofloxacin), 12.6% for amikacin (120/951) and 11.6% for kanamycin (106/914).

The study has several limitations, because it is based on programmatic information in a setting where it is not possible to perform a complete DST for each patient. Furthermore, although performed in quality-controlled

TABLE 1 Nationwide resistance to the drugs composing the World Health Organization “shorter” regimen in Brazil, 2000–2015

Drug tested	2000–2010		2011–2015		p-value	Overall 2000–2015	
	Resistant/ tested n	Resistant % [95% CI]	Resistant/ tested n	Resistant % [95% CI]		Resistant/ tested n	Resistant % [95% CI]
Pyrazinamide	1025/1989	51.5 [44.3–53.7]	449/961	46.7 [43.6–49.9]	0.01	1474/2950	50.0 [48.2–51.8]
Ethambutol	1177/3103	37.9 [36.2–39.6]	934/3305	28.3 [26.8–29.8]	<0.0001	2111/6408	32.9 [31.8–34.1]
Fluoroquinolones[#]	30/100	30.0 [21.0–39.0]	339/972	34.9 [31.9–37.9]	0.33	369/1072	34.4 [31.6–37.3]
<i>Levofloxacin</i>	2/7	28.6 [–4.9–62.1]	3/19	15.8 [–0.6–32.2]	0.59	5/26	19.2 [4.1–34.3]
<i>Moxifloxacin</i>	2/3	66.7% [13.4–120.0]	8/19	42.1 [19.9–64.3]	0.57	10/22	45.5 [24.7–66.3]
<i>Ofloxacin</i>	28/96	29.2 [20.1–38.3]	332/960	34.6 [31.6–37.6]	0.29	360/1056	34.1 [31.2–37.0]
Amikacin	14/88	15.9 [8.3–23.5]	120/951	12.6 [10.5–14.7]	0.38	134/1039	12.9 [10.9–14.9]
Kanamycin	6/27	22.2 [6.5–37.9]	106/914	11.6 [9.5–13.7]	0.09	112/941	11.9 [9.8–14.0]
Ethionamide	464/1564	29.7 [27.4–32.0]	24/126	19.1 [12.2–26.0]	0.01	488/1690	28.9 [26.7–31.0]

[#]: resistance to any fluoroquinolone.

laboratories belonging to the WHO network, the reliability of DST for some of the drugs tested (pyrazinamide and ethionamide, among others) requires some caution in evaluating the data. Finally, we cannot exclude a selection bias related to the limited DST coverage for some of the drugs.

However, the database is quality-controlled and contains a large number of comprehensive nationwide records (over 6000 cases) from a high-TB-burden country. To our knowledge, this is the first nationwide report on the drug resistance profile of the drugs composing the WHO “shorter” regimen in a high-burden country.

The study results allow us to draw some important conclusions.

First, that the programmatic approach to MDR-TB through standardised regimens seems not to have contributed to increasing the prevalence of resistance to the drugs used [13].

Secondly, although the data available in Brazil do not allow us to exactly predict the proportion of patients who are eligible for the shorter regimen, it is very likely to be higher than that recently reported in Europe (10%) and Pakistan (50%) [9–12]. Considering that i) about 30% of the cases tested for fluoroquinolones are resistant to it, ii) recently, about 12% of patients were found to be resistant to second-line injectables (although not all *Mycobacterium tuberculosis* strains were tested for fluoroquinolones and second-line injectables), and iii) there is apparently no increase in resistance trend, we might optimistically assume that up to 50–55% of the MDR-TB population in Brazil is likely to be susceptible to both fluoroquinolones and injectables and, therefore, potentially suitable for the “shorter” regimen. It is, therefore, mandatory that susceptibility to the drugs composing the regimen is confirmed before prescribing it.

A recent study demonstrated that the “shorter” regimen might reduce, in 8 years, the MDR-TB incidence by between –23% and –2% based on several assumptions, including the long-term efficacy of the “shorter” regimen, the degree of scale-up of MDR-TB treatment, and the likely transmission of *M. tuberculosis* drug-resistant strains within the community [14, 15]. The results of this study contribute to complement the available evidence.

Thirdly, in agreement with the WHO recommendations [8], it is important that national TB programmes in countries such as Brazil expand their capacity for rapid molecular testing (MTBDRsl) and DST for second-line drugs (at least fluoroquinolones and injectables) to enable clinicians to prescribe the “shorter” regimen to the right patients.

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References

- 1 Diel R, Vandeputte J, de Vries G, *et al.* Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. *Eur Respir J* 2014; 43: 554–565.
- 2 Migliori GB, Sotgiu G, Gandhi NR, *et al.* Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013; 42: 169–179.
- 3 Falzon D, Gandhi N, Migliori GB, *et al.* Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J* 2013; 42: 156–168.
- 4 Aung KJ, Van Deun A, Declercq E, *et al.* Successful ‘9-month Bangladesh regimen’ for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis* 2014; 18: 1180–1187.
- 5 Kuaban C, Noeske J, Rieder HL, *et al.* High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis* 2015; 19: 517–524.
- 6 Piubello A, Harouna SH, Souleymane MB, *et al.* High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis* 2014; 18: 1188–1194.
- 7 Van Deun A, Maug AK, Salim MA, *et al.* Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010; 182: 684–692.
- 8 World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis. 2016 Update. WHO/HTM/TB/2016.04. Geneva, World Health Organization, 2016.

- 9 Sotgiu G, Tiberi S, D'Ambrosio L, *et al.* Faster for less, the new 'shorter' regimen for multidrug-resistant tuberculosis. *Eur Respir J* 2016; 48: 1503–1507.
- 10 van der Werf MJ, Hollo H, Ködmön C, *et al.* Eligibility for shorter treatment of multidrug-resistant tuberculosis in the European Union. *Eur Respir J* 2017; 49: 1601992.
- 11 Sotgiu G, Tiberi S, D'Ambrosio L, *et al.* WHO recommendations on shorter treatment of multidrug-resistant tuberculosis. *Lancet* 2016; 387: 2486–2487.
- 12 Javaid A, Ahmad N, Khan AH, *et al.* Applicability of World Health Organization's recommended new shorter regimen in a multidrug-resistant tuberculosis high burden country. *Eur Respir J* 2017; 49: 1601967.
- 13 Dalcolmo MP, Fortes A, Melo FF, *et al.* Estudo de efetividade de esquemas alternativos para o tratamento da tuberculose multirresistente no Brasil. *Jornal de Pneumologia* 1999; 25: 70–77.
- 14 Kendall EA, Anthony T, Fojo AT, *et al.* Expected impact of adopting a 9-month regimen for multidrug-resistant tuberculosis: a population model. *Lancet Respir Med* 2016; in press [[https://doi.org/10.1016/S2213-2600\(16\)30423-4](https://doi.org/10.1016/S2213-2600(16)30423-4)].
- 15 Sotgiu G, Migliori GB. Effect of the short-course regimen on the global epidemic of multidrug-resistant tuberculosis. *Lancet Respir Med* 2016; in press [[https://dx.doi.org/10.1016/S2213-2600\(16\)30432-5](https://dx.doi.org/10.1016/S2213-2600(16)30432-5)].

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Author Queries

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- Q1 It has specified that this is th Brazilian national register; please check and amend as needed.
- Q2 By “this study”, are you referring to the present study, or the “recent study” mentioned in the previous sentence? Please clarify.
- Q3 Please indicate the significance of the italics in table 1.

Q1: Yes, it is correct

Q2: We are referring to the present study

Q3: Levofloxacin, Moxifloxacin , Ofloxacin are in italics because they belong to the fluoroquinolones group