

## Shortened multidrug-resistant tuberculosis treatment in settings with a high prevalence of ofloxacin resistance

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1 **TITLE:**

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19 LG, FV, HH, MB, MR, CDM contributed to the design of the manuscript

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25 **TEXT:**

26 We have read with interest the research letter by Javaid et al. in a recent issue of the European  
27 Respiratory Journal.<sup>1</sup> The authors aptly note some uncertainty in current World Health  
28 Organization (WHO) guidelines.<sup>2</sup> Nevertheless, we question the authors' main assertion that  
29 "high prevalence of ofloxacin resistance should not limit the applicability of the new shorter  
30 regimen". The shortened regimen has indeed produced promising results in a number of  
31 settings, in populations carefully selected for their limited exposure and resistance to second-  
32 line drugs.<sup>3-5</sup> That this should be extended to settings with high prevalence of fluoroquinolone  
33 resistance, without individual, rapid molecular testing for fluoroquinolone resistance, is not  
34 supported by data or WHO.

35 The present sub-national, cross-sectional study shows worryingly high levels of  
36 resistance to ofloxacin and other drugs contained in the shortened multidrug-resistant  
37 tuberculosis (MDR-TB) regimen. We concur with the authors on the importance of  
38 strengthening the public-health response to the various sources of fluoroquinolone-resistant  
39 TB in Pakistan. Nevertheless, the presence of ofloxacin resistance, tested at  $2 \mu\text{g}\cdot\text{mL}^{-1}$ , in  
40 48.6% of patients does not support widespread applicability of the shortened regimen in this  
41 population. More than 50% of the patients in Bangladesh with "high-level" resistance to  
42 ofloxacin by this definition had unfavorable treatment outcomes on the shortened regimen.<sup>3</sup>  
43 Moreover, it is noteworthy that the present study did not report overlapping resistance  
44 among these drugs to further inform estimates of the population eligible for the shortened  
45 regimen. Since rapid, reliable pyrazinamide testing is not available routinely, any use of the  
46 shortened regimen in the presence of high population levels of ofloxacin resistance needs to  
47 consider the frequency of concurrent pyrazinamide resistance: according to results from  
48 meta-analyses that supported the development of WHO recommendations, the probability of

49 favorable outcomes on the shortened regimen is reduced from 90.3 (95% CI: 87.8-92.4%)  
50 among all patients to 67.9% (95% CI: 47.5-84.1%) among patients with isolates resistant to  
51 both drugs.<sup>6</sup> The authors assertion that “it is not recommended to base decision-making on  
52 the basis of resistance to pyrazinamide and ethambutol” is at odds with these findings and  
53 with WHO guidance. The latter recommends avoiding the shortened treatment in patients  
54 with “documented or likely resistance to medicines in the regimen” and “in patients infected  
55 with strains known or strongly suspected of being resistant to one or more drugs in the shorter  
56 MDR-TB treatment regimen (e.g. pyrazinamide) ...”.<sup>6</sup>

57         The authors propose to increase the applicability of the shortened regimen in this and  
58 similar settings by: a) increasing the clinical breakpoint for ofloxacin from 2 to 4  $\mu\text{g}\cdot\text{mL}^{-1}$ , b)  
59 administering moxifloxacin at high dose, and c) considering resistance to  
60 moxifloxacin/gatifloxacin, rather than ofloxacin, as an exclusion criterion for the short course  
61 treatment. However, these changes neither resolve the uncertainty in the guidelines nor  
62 strengthen the case for the shortened regimen in populations with high prevalence of  
63 fluoroquinolone resistance. First, rationale for the proposed increase of MIC for ofloxacin,  
64 presumably to serve as a better proxy for resistance to later-generation fluoroquinolones, is  
65 not presented; this cut-off is higher than that used for both the national survey and the  
66 observational study that demonstrated different clinical outcomes of the shorter regimen in  
67 strains with low-level versus high-level fluoroquinolone resistance.<sup>3,7</sup> Second,  
68 moxifloxacin/gatifloxacin are already prescribed at high dose (400 to 800 mg/day according  
69 to weight group) in some applications of the shortened regimen, so the results showing  
70 reduced effectiveness in the presence of resistance to fluoroquinolones and pyrazinamide  
71 already factor in this reinforcement.<sup>6</sup> Third, while we agree in principle that usefulness of late-  
72 generation fluoroquinolones is best guided by drug susceptibility testing (DST) to those

73 drugs—and not by DST to earlier-generation class members<sup>8</sup>—the proposed modification to  
74 guidance to rule out moxifloxacin/gatifloxacin resistance is problematic from an operational  
75 standpoint; DST to these drugs is infrequently available in high-burden settings (including  
76 Pakistan, according to the authors). More practically, rapid molecular tests will be used to  
77 assess eligibility. Their careful interpretation to identify individual patients eligible for the  
78 shortened regimen will be especially important in settings with known high population levels  
79 of fluoroquinolone resistance. Existing data from sequencing suggest that resistance caused  
80 by mutations in the QRDR region of *gyrA* (except 94Ala) is associated with an important  
81 increase in poor outcomes on the shortened regimen.<sup>9</sup> Fortunately, there are other options:  
82 the advent of delamanid and bedaquiline,<sup>10</sup> as well as other “core” MDR-TB drugs used in  
83 conventional regimens offer alternatives to using the shortened regimen in patients in whom  
84 its success is likely compromised. Multiple new studies of shortened regimens containing  
85 these drugs (Nix-TB [NCT02333799], TB-PRACTECAL [NCT02589782], endTB [NCT02754765])  
86 may generate palatable and effective alternatives.

87         In conclusion, we recommend caution in the introduction of the shortened MDR-TB  
88 treatment in settings with high prevalence of resistance to ofloxacin or pyrazinamide;  
89 eligibility for shortened treatment should be evaluated individually according to rapid  
90 molecular testing and available DST results.

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