Shortened multidrug-resistant tuberculosis regimens overcome low-level fluoroquinolone resistance

To the Editor:

We read the research letter by Javaid *et al.* [1] with great interest. The recommendations from the World Health Organization (WHO) on the use of shortened multidrug-resistant tuberculosis (MDR-TB) regimens controversially indicated that "shortened MDR-TB regimens should not be used in patients who have documented or likely resistance to medicines in the regimen" [2], leading to the concept that MDR-TB patients with additional resistance to not only fluoroquinolones (FQs) or second-line injectables (SLIs), but also ethambutol (EMB), prothionamide (Pto) and pyrazinamide (PZA) would not be eligible for the regimens [3]. This is a highly conservative approach that will greatly limit the applicability of shortened MDR-TB regimens and deprive many MDR-TB patients in high-burden countries of short and highly effective regimens. The 9-month MDR-TB regimen piloted in Bangladesh comprised high-dose gatifloxacin (^{h}Gfx), clofazimine (Cfz), EMB and PZA throughout, supplemented by kanamycin (Km), Pto and high-dose isoniazid (^{h}INH) during an intensive phase [4]. The regimen was initially designed to be used in settings with limited resources, where drug susceptibility testing was not available in a timely manner. It was designed as a standardised regimen, using clofazimine and first-line drugs to replace toxic and less effective second-line drugs such as cycloserine and para-aminosalicylic acid. The drugs that are crucial in achieving sputum conversion are ^{h}Gfx and Km, and those crucial in shortening the duration of treatment are ^{h}Gfx, Cfz and PZA [5]. Other drugs, in combination, play a supportive role and full susceptibility to these drugs was not expected in the original design. Most patients treated with shortened MDR-TB regimens in Bangladesh [4] and other countries [6] have been exposed to EMB for a prolonged period. Those with resistance to EMB were not excluded and replacement of EMB by another drug was not performed. ^{h}INH and Pto were combined complimentarily to address cross-resistance to Pto in *inhA*-mutant strains of *Mycobacterium tuberculosis*, since the serum level of ^{h}INH will exceed the minimum inhibitory concentration (MIC) of strains with *inhA* mutation by a wide margin, ensuring that at least one of ^{h}INH and Pto will be effective in most cases. Resistance to Pto was not associated with an unfavourable outcome [4] and ^{h}INH may also be able to suppress a substantial proportion of bacilli with *katG* mutation.

Shortened MDR-TB regimens using ^{h}Gfx overcome low-level FQ resistance. In Bangladesh [4], high-level Gfx resistance (MIC $\geqslant 2\ mg{\cdot}L^{-1}$) but not low-level resistance was significantly associated with bacteriologically unfavourable outcomes (failure or relapse 36.4% *versus* 3.2%). Another study enrolled a larger number of MDR-TB cases in Bangladesh treated with Gfx, including those analysed by Aung *et al.* [4] and second-line retreatment cases with a higher prevalence of FQ resistance [7]. With this selection, the proportion of failure/relapse rose from 4% with Gfx MIC $<1\ mg{\cdot}L^{-1}$ to 18%, 48% and 100% with MIC 1 (low-level), 2–4 (medium) and $>4\ mg{\cdot}L^{-1}$ (high), respectively. Table 1 shows the average level of resistance and the proportion of Bangladeshi patients with bacteriologically adverse outcomes by *gyrA/B* mutation pattern [7].

A considerable proportion of FQ-resistant cases can still reach relapse-free cure with the unmodified short MDR-TB regimen. Using high-dose moxifloxacin (or ^{h}Gfx) is crucial to overcome low-level FQ resistance [8]. The poorer outcomes in the second study may be explained by the inclusion of previously second-line treated cases with longstanding selection pressure leading to increased MICs.

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TABLE 1 Resistance level and impact on treatment outcome of individual *gyrA/B* mutations

Mutation	FQ resistance level	Failure/relapse outcome
gyrA^{94Ala}	Low or medium	11%
gyrA^{90Val}	Medium	47%
gyrA^{94Gly}	High	70%
gyrA^{94Tyr}	High	100%
gyrA^{88Cys}	High	Unknown
gyrA^{89Asn}	High	Unknown
gyrA^{91Pro}	High	Unknown
gyrA$^{94Asn/His}$	High	Unknown
gyrB^{538Ser}	High	Unknown
gyrB^{540Arg}	High	Unknown
Multiple mutations	High	Unknown

FQ: fluoroquinolone. Reproduced and modified from [7] with permission from the publisher.

Molecular test systems have made drug-susceptibility testing (DST) accessible for most patients. Recent comparisons with phenotypic DST have made it clear that molecular tests may also be more accurate than the gold standard, leading mainly to an underestimated specificity of molecular tests. For the core first- or second-line drugs, rifampicin and FQs, molecular tests have been proposed as an alternative or complementary part of the gold standard [9, 10]. The WHO has recently recommended the new version 2 of GenoType MTBDRsl lineprobe assay (LPA) (Hain Lifescience GmbH, Nehren, Germany) for detection of resistance to FQs and SLIs. An independent evaluation showed superiority of the new version, with sensitivity for FQ resistance reaching 95% and specificity, 98%. The LPA banding pattern allows the identification of the most frequent mutations. For *gyrA*, low- to medium-level resistance is shown by a MUT 1 or MUT3A band, while high-level alerts are the absence of WT1 without MUT1 showing, MUT2, MUT3B, C or D, and absence of WT3 without a MUT band. Both *gyrB* MUT1 and MUT2 bands indicate high resistance, as do multiple mutations at one or both loci. This might be applied under programme conditions to guide the application of shortened MDR-TB regimens. As long as they remain susceptible to an injectable, effective treatment of cases with low-level resistance to FQs with the shortened regimens thus remains possible. JAVAID *et al.* [1] pointed out that in Pakistan, this means the large majority of FQ-resistant MDR-TB cases. For cases with medium- or high-level resistance, replacing the FQs with a new drug, such as bedaquiline, is likely the best option.

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