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Initial resistance to companion drugs should not be considered an exclusion criterion for the shorter multidrug-resistant tuberculosis treatment regimen

Pauline Lempens[a,b,*], Tom Decroo[c], Kya J.M. Aung[d], Mohammad A. Hossain[d], Leen Rigouts[a,b], Conor J. Meehan[a,1], Armand Van Deun[e], Bouke C. de Jong[a]

[a] Unit of Mycobacteriology, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[b] Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium
[c] Unit of HIV/AIDS and Infectious Diseases, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[d] Damien Foundation, Dhaka, Bangladesh
[e] Independent Consultant, Leuven, Belgium

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ABSTRACT

Objectives: We investigated whether companion drug resistance was associated with adverse outcomes of the shorter multidrug-resistant tuberculosis (MDR-TB) treatment regimen in Bangladesh after adjustment for fluoroquinolone resistance.
Methods: MDR/rifampicin-resistant (RR) tuberculosis patients registered for treatment with a standardized gatifloxacin-based shorter MDR-TB treatment regimen were selected for the study. Drug resistance was determined by the proportion method, gatifloxacin and isoniazid minimum inhibitory concentration testing for selected isolates, and whole genome sequencing.
Results: Low-level and high-level fluoroquinolone resistance were the most important predictors of adverse outcomes, with pyrazinamide resistance having a significant yet lower impact. In patients with fluoroquinolone-/second-line injectable-susceptible tuberculosis, non-eligibility for the shorter MDR-TB treatment regimen (initial resistance to pyrazinamide, ethionamide, or ethambutol) was not associated with adverse outcome (adjusted odds ratio 1.01; 95% confidence interval 0.4–2.8). Kanamycin resistance was uncommon (1.3%). Increasing levels of resistance to isoniazid predicted treatment failure, also in a subgroup of patients with high-level fluoroquinolone-resistant tuberculosis.
Conclusions: Our results suggest that resistance to companion drugs in the shorter MDR-TB treatment regimen, except kanamycin resistance, is of no clinical importance as long as fluoroquinolone susceptibility is preserved. Hence, contrary to current WHO guidelines, exclusions to the standard regimen are justified only in the case of fluoroquinolone resistance and possibly kanamycin resistance.

Introduction

Ideally, a tuberculosis (TB) treatment regimen includes a core drug that drives the efficacy of the regimen, and companion drugs with either bactericidal or sterilizing activity (Van Deun et al., 2018). Based on these principles, the so-called shorter regimen for the treatment of multidrug-resistant TB (MDR-TB) was developed in Bangladesh two decades ago (Aung et al., 2014; Van Deun et al., 2010). It used later-generation fluoroquinolones (either gatifloxacin or levofloxacin) as the core drug and kanamycin as the main drug protecting against acquisition of resistance to the core drug. Companion drugs were included to help prevent acquired resistance to the fluoroquinolone and kanamycin (Van Deun et al., 2018). Prothionamide was included because it has also bactericidal activity, and pyrazinamide and clofazimine were included because they help in sterilization. Isoniazid was expected to often have some remaining activity, contributing to the effectiveness of the regimen to a highly variable extent. The same is true for the bacteriostatic ethambutol, to which most MDR strains showed resistance at that time (Van Deun et al., 2018).

* Corresponding author at: Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium.
E-mail address: plempens@itg.be (P. Lempens).
[1] Present address: School of Chemistry and Biosciences, University of Bradford, Bradford, UK.

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The shorter treatment regimen has since been successfully implemented in many countries worldwide. Resistance to fluoroquinolones has been found to be the major predictor of adverse treatment outcome (Rigouts et al., 2016; Trébucq et al., 2019; Van Deun et al., 2019). The importance of resistance to the other drugs in the regimen is insufficiently understood (Trébucq et al., 2019). Originally designed as a standardized regimen in a low-resource setting, the shorter treatment regimen was administered without prior drug susceptibility testing (DST). Full susceptibility to all companion drugs was not counted on, because their individual activity was not considered essential for high success rates. Moreover, the regimen was considered as part of a cascade of regimens, with a next-level core drug regimen for retreatment of the expected few failure and relapse cases (Van Deun et al., 2018). Nevertheless, current WHO guidelines for the treatment of MDR-TB recommend to use resistance to any of the drugs in the regimen, except isoniazid, as an exclusion criterion for the shorter MDR-TB treatment regimen (WHO, 2019c).

Recently published extensive data on companion drug resistance suggest that the effect of resistance to companion drugs in the shorter MDR-TB treatment regimen on outcome is rather limited (Piubello et al., 2020). However, in this cohort, very few patients had an adverse bacteriological outcome (12/249; 8 failure and 4 relapse), limiting the estimation of predictors of poor outcome. Moreover, kanamycin resistance is quite rare in most settings where the regimen has been studied, restricting analyses of its association with adverse outcome (Trébucq et al., 2019). A recent individual patient data meta-analysis found that, except in low-income settings, kanamycin worsened MDR-TB treatment outcomes, which led to the WHO recommendation to stop using kanamycin (Ahmad et al., 2018; WHO, 2019c). Unfortunately, the meta-analysis neglected to check the effectiveness of injectables for prevention of acquired resistance to the core drug. Moreover, the adverse outcomes with use of kanamycin were from high-income settings only, and these results contradicted those of the previous meta-analysis by the same group that found greater survival with longer use of injectables, leading to the 2014 WHO guidelines recommending injectables for at least the first 8 months (Ahuja et al., 2012; WHO, 2014). Most likely this has led to excessively frequent ototoxicity, which is inevitable with prolonged use of these drugs, that has provoked the sudden aversion to any use of these standard TB drugs and their replacement by a new core drug with still many unknowns; that is, bedaquiline (WHO, 2019c).

A study on the implementation of the shorter MDR-TB treatment regimen in nine African countries found that isoniazid susceptibility was associated with a significantly lower risk of bacteriological failure. Since testing for isoniazid resistance is still difficult and often not done, this is another reason to use isoniazid indiscriminately for all rifampicin-resistant TB (RR-TB; Schwœbel et al., 2020; Trébucq et al., 2018). Resistance also to isoniazid (MDR-TB) is highly prevalent in RR-TB isolates (WHO, 2019a), but the frequency of the highest level of resistance, conferred by double mutations in *katG* and *inhA* (Ghodousi et al., 2019; Lempens et al., 2018), is low (<5% in most settings) (Seifert et al., 2015), and the association between different levels of resistance to the drug and treatment outcome remains unclear.

In this study, we investigated a large cohort of MDR-TB patients from Bangladesh to assess whether resistance to companion drugs is associated with adverse outcome of the shorter MDR-TB treatment regimen after adjustment for fluoroquinolone resistance. Moreover, whole genome sequencing (WGS) data for this cohort enabled us to look into drug resistance in greater detail.

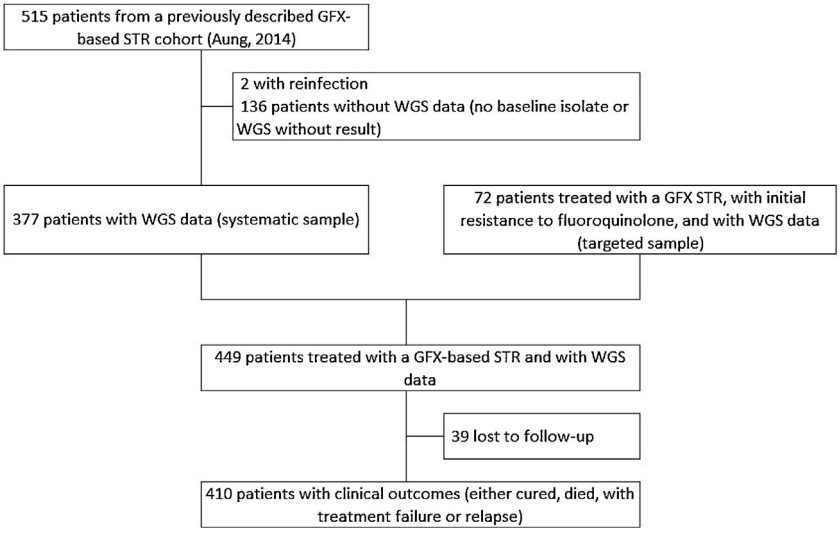

Figure 1. Flowchart showing the number of patients included in the analysis. Patients were registered for treatment in the Damien Foundation MDR-TB project area in Bangladesh between March 2005 and March 2015. For the analysis in Table 5, only patients of the cohort described by Aung et al. (2014) with a clinical outcome (342 patients = 377 patients − 35 patients lost to follow-up) were included. FQ, fluoroquinolones; GFX, gatifloxacin; STR, shorter multidrug-resistant tuberculosis treatment regimen; WGS, whole genome sequencing.

Table 1
Summary of the variables included in the study, stratified by initial fluoroquinolone (FQ) resistance.

	Total		Initial FQ resistance					
			FQ S		FQ R low		FQ R high	
	N	%	*N*	%	*N*	%	*N*	%
	449		352		26		71	
Gender								
Female	133	29.6	101	28.7	7	26.9	25	35.2
Male	316	70.4	251	71.3	19	73.1	46	64.8
Age group (years)								
10 to <20	47	10.5	35	9.9	4	15.4	8	11.3
20 to <30	152	33.9	108	30.7	10	38.5	34	47.9
30 to <40	104	23.2	92	26.1	4	15.4	8	11.3
40 to <50	75	16.7	59	16.8	6	23.1	10	14.1
50 to <60	45	10.0	37	10.5	1	3.8	7	9.9
≥60	26	5.8	21	6.0	1	3.8	4	5.6
Initial KAN resistance								
No	443	98.7	352	100	25	96.2	66	93.0
Yes	6	1.3	0	0	1	3.8	5	7.0
Initial INH resistance (gDST)								
S	23	5.1	21	6.0	0	0	2	2.8
R low	23	5.1	19	5.4	1	3.8	3	4.2
R moderate	358	79.7	281	79.8	21	80.8	56	78.9
R high	45	10.0	31	8.8	4	15.4	10	14.1
Initial INH resistance (pDST)								
S	5	1.1	5	1.4	0	0	0	0
R low	17	3.8	15	4.3	1	3.8	1	1.4
R moderate	48	10.7	0	0	3	11.5	45	63.4
R high	18	4.0	0	0	2	7.7	16	22.5
Level of INH resistance unknown	361	80.4	332	94.3	20	76.9	9	12.7
Initial INH resistance (gDST and pDST)								
S	4	0.9	4	1.1	0	0	0	0
R low	17	3.8	15	4.3	1	3.8	1	1.4
R moderate	48	10.7	1	0.3	3	11.5	44	62.0
R high	19	4.2	0	0	2	7.7	17	23.9
Level of INH resistance unknown	361	80.4	332	94.3	20	76.9	9	12.7
Initial EMB resistance								
No	148	33.0	129	36.6	4	15.4	15	21.1
Yes	301	67.0	223	63.4	22	84.6	56	78.9
Initial PZA resistance								
No	302	67.3	254	72.2	13	50.0	35	49.3
Yes	147	32.7	98	27.8	13	50.0	36	50.7
Initial ETH resistance								
No	344	76.6	274	77.8	17	65.4	53	74.6
Yes	105	23.4	78	22.2	9	34.6	18	25.4
Initial CFZ resistance								
No	449		352		26		71	
Outcomes								
Cure	344	76.6	292	83.0	20	76.9	32	45.1
Completion	12	2.7	10	2.8	0	0	2	2.8
Failure	19	4.2	1	0.3	2	7.7	16	22.5
Relapse	8	1.8	0	0	2	7.7	6	8.5
Death	27	6.0	20	5.7	0	0	7	9.9
LTFU	39	8.7	29	8.2	2	7.7	8	11.3
Programmatic effectiveness								
Success	356	79.3	302	85.8	20	76.9	34	47.9
Adverse (death, LTFU, FL, or RL)	93	20.7	50	14.2	6	23.1	37	52.1
Clinical effectiveness								
Success	356	86.8	302	93.5	20	83.3	34	54.0
Adverse (death, FL, or RL)	54	13.2	21	6.5	4	16.7	29	46.0
Sample								
Systematic	377	84.0	352	100	13	50.0	12	16.9
Targeted	72	16.0	0	0	13	50.0	59	83.1

CFZ, clofazimine; EMB, ethambutol; ETH, ethionamide; FL, failure; gDST, genotypic drug susceptibility testing; high, high level; INH, isoniazid; KAN, kanamycin; LTFU, lost to follow-up; low, low level; moderate, moderate level; pDST, phenotypic drug susceptibility testing; PZA, pyrazinamide; R, resistant; RL, relapse; S, susceptible.

Materials and methods

Study setting

The study was conducted in the Damien Foundation MDR-TB project area in Bangladesh, which spans 13 of 64 districts of the country. In 2018, the incidence rate of TB in Bangladesh was 221 cases per 100,000, with an HIV prevalence in incident TB patients of 0.20%. The incidence rate of MDR/RR-TB was 3.7 cases per 100,000 (WHO, 2019a).

Study design

This was a retrospective cohort study.

Study population

Between March 2005 and March 2015, 943 gatifloxacin-based shorter MDR-TB treatment regimen episodes for MDR/RR-TB patients were registered. Besides the systematic sample including patients of the previously described Bangladesh MDR-TB cohort (Aung et al., 2014), patients with fluoroquinolone-resistant MDR/RR-TB were selected to specifically study the effect of resistance to companion drugs on treatment outcome (i.e. targeted sample) (Figure 1).

Treatment

Patients were treated with the shorter MDR-TB treatment regimen consisting of high-dose gatifloxacin (up to 800 mg for those weighing more than 50 kg), clofazimine, ethambutol, and pyrazinamide for 9–11 months, supplemented with high-dose isoniazid (10 mg/kg), kanamycin, and prothionamide during the intensive phase of 4–6 months (the intensive phase was extended by 1 or 2 months if there was no smear conversion after 4 or 5 months). Further treatment details as well as treatment outcome definitions used have been described previously (Aung et al., 2014; Van Deun et al., 2010). Reinfection was distinguished from relapse by spoligotype analysis, and by MIRU-VNTR if spoligotypes were identical.

Drug susceptibility testing

A detailed description of the final classification rules for drug resistance (level) per drug is given in Supplementary Table 1.

Phenotypic drug resistance was determined by the proportion method on Löwenstein-Jensen (LJ) medium (isoniazid 0.2, 1.0, and 5.0 mg/L, ethambutol 2 mg/L) and Middlebrook 7H11 agar (ofloxacin 2.0 and 8.0 mg/L, kanamycin 6.0 mg/L, ethionamide 10.0 mg/L). In addition, gatifloxacin minimum inhibitory concentration (MIC) (0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 mg/L on LJ medium) was determined for isolates with resistance to ofloxacin at 2.0 mg/L, and isoniazid MIC (1.6, 3.2, 6.4, 12.8, 19.2, and 25.6 mg/L on LJ medium) was determined for isolates with high-level resistance to ofloxacin at 8.0 mg/L.

Genotypic resistance was determined by WGS. A subset of isolates (n = 47) was included in our earlier publication on the association between genotypic and phenotypic isoniazid resistance, and their WGS was described there (Lempens et al., 2018). For the remaining samples, genomic DNA (gDNA) was extracted by a combined enzymatic and mechanical extraction procedure (Lempens et al., 2018). WGS was done at the Translational Genomics Research Institute through the ReSeqTB sequencing platform (Starks et al., 2015). Microbial classification of the reads was done with Centrifuge (Kim et al., 2016) and non-*Mycobacterium tuberculosis* (MTB) reads were removed. Isolates were marked as contaminated and were subsequently excluded if the percentage of non-MTB reads was greater than 10%. The MTBseq pipeline was used for quality control of the MTB reads, and isolates failing quality control (i.e. < 90% coverage of the reference genome or average sequencing depth <30×) were excluded (Kohl et al., 2018). Read trimming and mapping as well as variant calling and annotation were done with command line version 2.8.12 of TBProfiler (Coll et al., 2015; Phelan et al., 2019). Annotated variants were reported if found at any frequency in the isolate (i.e. minority populations conferring heteroresistance) and if present in the literature-based TBProfiler library database (https://github.com/jodyphelan/tbdb) accessed on 15 July 2020. Genomic variants associated with drug resistance having a sequencing depth below the default threshold of 10× but greater than 1× were included in the analysis. They were frequently found at certain common drug resistance positions, and for drugs with additional susceptibility information, their presence was supported by Sanger sequencing, line probe assay, and/or phenotypic DST (pDST) results.

Data availability

WGS reads are available in the European Nucleotide Archive (PRJEB39569). Variables included in the analysis are provided in Supplementary Table 2. Moreover, WGS reads, as well as pDST and clinical data, are included in the ReSeqTB data platform and are accessible on registration at https://platform.reseqtb.org/.

Statistics

The chi-square test or Fisher's exact test was used to identify associations between categorical variables. We used Firth multivariable logistic regression models to estimate the correlation between variables of interest showing initial resistance (for ethambutol, fluoroquinolones, isoniazid (pDST alone, genotypic DST (gDST) alone, and a composite variable of both pDST and gDST), kanamycin, ethionamide (results apply to prothionamide as the drug in the shorter treatment regimen), and pyrazinamide) and outcome variables, including "clinically adverse outcome" (failure, relapse, or death), "bacteriologically adverse outcome" (either failure or relapse), and treatment failure only. We adjusted for the presence of initial fluoroquinolone resistance, which is known to be the most important predictor of adverse outcome in patients treated with the shorter treatment regimen (Van Deun et al., 2019), and the sampling approach (systematic vs targeted). When DST results were not complete for a variable of interest, we performed a complete case analysis, including only those patients with no missing data for the variables of interest. We used Stata version 14.2 (StataCorp, USA).

Ethics

All patients starting the shorter MDR-TB treatment regimen provided written informed consent. Ethics approval for the present deidentified analysis was provided by the Institute of Tropical Medicine institutional review board.

Results

Patient and bacteriological characteristics

Of 515 patients included in our previous publication (Aung et al., 2014), WGS data were available for 377 patients (73.2%) (Figure 1). We added data from 72 patients with initial resistance to fluoroquinolones and treated with a gatifloxacin-based regimen to obtain an analysis population of 449 patients.

Table 2
Correlation between genotypic and phenotypic isoniazid susceptibility testing in 88 patients with data available for both methods.

	Total	Phenotypic DST level of resistance				
		S	Low	Moderate	High	No data
Susceptible on gDST						
wild type	21	4	9	0	0	8
ahpC-52C>T	1	0	0	0	0	1
ahpC-81C>T	1	0	0	0	1	0
Low-level resistance on gDST						
fabG1 -15C>T	1	0	0	1	0	0
fabG1-15C>T[a]	13	0	6	0	0	7
fabG1-17G>T	1	0	0	1	0	0
fabG1-8T>C	1	0	1	0	0	0
inhA Ile194Thr[a]	3	0	0	0	1	2
i*nhA* Ile21Val	2	0	1	0	0	1
i*nhA* Ser94Ala	2	0	0	0	0	2
Moderate-level resistance on gDST						
ahpC-48G>A, *katG* Ser315Thr	1	0	0	0	0	1
fabG1 -15C>T[a], *inhA* Ile194Thr[a]	3	0	0	0	0	3
fabG1 -15C>T[a], *inhA* Ser94Ala[a]	1	0	0	0	0	1
fabG1 -15C>T, *inhA* Ser94Ala	1	0	0	0	1	0
fabG1 -8T>A[a], *inhA* Ile194Thr[a]	1	0	0	0	0	1
inhA Ile21Thr, *fabG1* -15C>T[a]	1	0	0	0	0	1
inhA Ile21Val, *fabG1* -15C>T[a]	3	0	0	0	0	3
inhA Ile21Val, *fabG1* -8T>A[a]	1	0	0	0	0	1
inhA Ser94Ala, *fabG1* -15C>T[a]	1	0	0	0	0	1
k*atG* Ala264Thr	2	0	0	0	0	2
k*atG* Asn138His	1	0	0	0	0	1
k*atG* Asn138Ser	2	0	0	0	0	2
k*atG* Ser315Asn	3	0	0	0	0	3
k*atG* Ser315Thr	337	1	0	45	7	284
High-level resistance on gDST						
fabG1 -15C>T[a], *katG* Ser315Gly[a], *inhA* Ile194Thr[a]	1	0	0	0	0	1
fabG1 -15C>T, *katG* Ser315Thr	1	0	0	0	1	0
katG 2153889_2156147del	1	0	0	0	0	1
katG 54_55insAC, *fabG1* -15C>T[a]	1	0	0	0	0	1
katG Met126Ile, *inhA* Ser94Ala[a]	1	0	0	1	0	0
katG Ser315Thr, *fabG1* -15C>T[a]	31	0	0	0	6	25
katG Ser315Thr, *inhA* Ser94Ala[a]	1	0	0	0	0	1
k*atG* Ser315Thr, *katG* Thr275Ala	5	0	0	0	1	4
k*atG* Trp397Ter	1	0	0	0	0	1
k*atG* Trp90Ter	1	0	0	0	0	1
katG Tyr155Cys, *inhA* Ile21Val	1	0	0	0	0	1
Total	449	5	17	48	18	361

DST, drug susceptibility testing; gDST, genotypic drug susceptibility testing; High, high-level resistance; Low, low-level resistance; Moderate, moderate-level resistance; S, susceptible.

[a] Genomic variants associated with drug resistance having a sequencing depth below the default threshold of 10× but greater than 1×, and with no heteroresistance (i.e. 100% of reads showed that allele).

Table 1 summarizes the variables included in the study, stratified by initial fluoroquinolone resistance. Most patients were male (70.4%). Of the 449 patients, 352 (78.4%) initially had fluoroquinolone-susceptible TB, 26 (5.8%) initially had low-level fluoroquinolone-resistant TB, and 71 (15.8%) initially had high-level fluoroquinolone-resistant TB. Of the 449 patients, 344 (76.6%) were cured, 12 (2.7%) completed treatment, 19 (4.2%) were identified as having treatment failure, 8 (1.8%) had relapse, 27 (6.0%) died, and 39 (8.7%) were lost to follow-up.

Frequency of initial resistance

Of the 449 patients, 301 (67.0%) had initial resistance to ethambutol, 147 (32.7%) had initial resistance to pyrazinamide, and 105 (23.4%) had initial resistance to ethionamide (Table 1). Initial kanamycin resistance was found in few patients ($n = 6$; 1.3%). High-level initial genotypic isoniazid resistance was found in 45 patients (10.0%) and high-level phenotypic resistance to isoniazid was found in 18 of 88 patients (20.5%) with pDST data. Data on the phenotypic level of isoniazid resistance were missing for 361 patients (80.4%). Table 2 shows all variants found in isoniazid-resistance-conferring genes, their classification as susceptible, low-level resistant, moderate-level resistant, and high-level resistant, and their pDST results. No clofazimine resistance was found.

Adverse outcomes

Not considering those lost to follow-up, 13.2% of patients (54/410) had a clinically adverse outcome (treatment failure, relapse, or death) (Table 3).

Among patients with initially fluoroquinolone-susceptible TB, 6.5% (21/323) experienced a clinically adverse outcome, compared with 16.7% (4/24) with low-level resistant TB and 46.0% (29/63) with high-level resistant TB (Table 3). We also found a correlation between clinical outcomes and level of initial resistance to isoniazid on pDST ($p = 0.02$), and resistance to isoniazid on a combination of pDST and gDST ($p = 0.02$). As the level of isoniazid resistance increased, the proportion with a successful outcome decreased, with 100%, 93.8%, 59.5%, and 50.0% success on pDST for

susceptible, low-level resistant, moderate-level resistant, and high-level resistant TB, respectively. Also pyrazinamide resistance was correlated with clinical outcome ($p < 0.001$). In the targeted sample, adverse outcomes were more likely ($p < 0.001$).

High-level fluoroquinolone resistance was associated with a clinically adverse outcome (vs fluoroquinolone-susceptible TB; adjusted odds ratio (aOR) 10.3; 95% confidence interval (CI) 3.1–35.0; $p < 0.001$) after adjustment for the sampling approach (Table 4). Initial pyrazinamide resistance (aOR 2.0; 95% CI 1.1–3.7; $p = 0.04$) was associated with a clinically adverse outcome after adjustment for initial fluoroquinolone resistance and the sampling approach. Initial resistance to other companion drugs did not predict clinically adverse outcomes.

Table 4 also shows predictors of bacteriologically adverse outcomes (either failure or relapse), with low-level fluoroquinolone resistance (aOR 34.1; 95% CI 4.3–271.6; $p = 0.001$), high-level fluoroquinolone resistance (aOR 83.9; 95% CI 10.4–673.9; $p < 0.001$), and pyrazinamide resistance (aOR 2.6; 95% CI 1.01–6.7; $p = 0.048$) predicting an adverse outcome.

Predictors of failure included only low-level and high-level fluoroquinolone resistance and ethionamide resistance. For every step increase between susceptibility, low-level resistance, moderate-level resistance, and high-level resistance to isoniazid, the odds of failure increased significantly on either pDST (aOR 3.6; 95% CI 1.01–12.9; $p = 0.048$) or a combination of pDST and gDST (aOR 3.6; 95% CI 1.02–12.8; $p = 0.047$). High-level isoniazid resistance (vs any other level) predicted treatment failure on either pDST (aOR 3.8; 95% CI 1.03–13.7; $p = 0.04$) or a combination of pDST and gDST (aOR 3.8; 95% CI 1.03–13.7; $p = 0.04$).

Among 342 patients belonging to the systematic sample and treated with the shorter treatment regimen, 81 (23.7%) were eligible based on WHO criteria (only initial resistance to isoniazid is allowed) (WHO, 2019b). Treatment success was 93.3% among 242 patients not eligible because of initial resistance to pyrazinamide, ethionamide, or ethambutol, which is similar to the 93.8% success among 81 patients eligible according to the WHO criteria, and higher than the 73.7% success among 19 patients with initial resistance to fluoroquinolones (Table 3).

In patients with initially fluoroquinolone-susceptible/second-line-injectable-susceptible TB, initial resistance to pyrazinamide, ethionamide, or ethambutol (leading to non-eligibility for the shorter treatment regimen according to WHO criteria) (WHO, 2019b) did not predict a clinically adverse outcome (aOR 1.01; 95% CI 0.4-2.8; $p = 1.0$; Table 4).

Table 3
Clinically adverse outcome (failure, relapse, or death) by initial resistance to drugs included in the shorter multidrug-resistant tuberculosis treatment regimen (STR).

	Total	Success		Failure		Relapse		Death		p[c]
	N	*N*	%	*N*	%	*N*	%	*N*	%	
	410	356	86.8	19	4.6	8	2.0	27	6.6	
FQ										<0.001
S	323	302	93.5	1	0.3	0	0	20	6.2	
R low	24	20	83.3	2	8.3	2	8.3	0	0	
R high	63	34	54.0	16	25.4	6	9.5	7	11.1	
KAN										0.001
S	404	354	87.6	16	4.0	8	2.0	26	6.4	
R	6	2	33.3	3	50.0	0	0	1	16.7	
INH (gDST)										0.5
S	20	19	95.0	0	0	0	0	1	5.0	
R low	22	20	90.9	2	9.1	0	0	0	0	
R moderate	330	285	86.4	13	3.9	7	2.1	25	7.6	
R high	38	32	84.2	4	10.5	1	2.6	1	2.6	
INH (pDST)[a]										0.02
S	5	5	100	0	0	0	0	0	0	
R low	16	15	93.8	0	0	0	0	1	6.3	
R moderate	42	25	59.5	6	14.3	6	14.3	5	11.9	
R high	18	9	50.0	8	44.4	1	5.6	0	0	
INH (gDST and pDST)[a]										0.02
S	4	4	100	0	0	0	0	0	0	
R low	16	15	93.8	0	0	0	0	1	6.3	
R moderate	43	26	60.5	6	14.0	6	14.0	5	11.6	
R high	18	9	50.0	8	44.4	1	5.6	0	0	
EMB										0.2
S	139	124	89.2	3	2.2	1	0.7	11	7.9	
R	271	232	85.6	16	5.9	7	2.6	16	5.9	
PZA										<0.001
S	275	250	90.9	8	2.9	1	0.4	16	5.8	
R	135	106	78.5	11	8.1	7	5.2	11	8.1	
ETH										0.06
S	316	276	87.3	10	3.2	7	2.2	23	7.3	
R	94	80	85.1	9	9.6	1	1.1	4	4.3	
Sample										<0.001
Systematic	342	316	92.4	3	0.9	1	0.3	22	6.4	
Targeted	68	40	58.8	16	23.5	7	10.3	5	7.4	
WHO STR eligibility[b]										0.003
Eligible	81	76	93.8	0	0	0	0	5	6.2	
Resistance to a companion drug	242	226	93.4	1	0.4	0	0	15	6.2	
Resistance to FQ (any level)	19	14	73.7	2	10.5	1	5.3	2	10.5	

EMB, ethambutol; ETH, ethionamide; FQ, fluoroquinolone; gDST, genotypic drug susceptibility testing; high, high level; INH, isoniazid; KAN, kanamycin; low, low level; moderate, moderate level; pDST, phenotypic drug susceptibility testing; PZA, pyrazinamide; R, resistant S, susceptible.

[a] Data on level of phenotypic isoniazid resistance were missing for 329 patients.

[b] Data from systematic sample only; In this subgroup no patients had tuberculosis initially resistant to second-line injectables; WHO eligible: no resistance to any of the STR components (except isoniazid).

[c] Fisher's exact test.

Table 4
Factors associated with having an adverse outcome.

	Success vs FL, RL, or death		Success vs FL or RL		Success vs FL	
	aOR N=410	95% CI	aOR N=383	95% CI	aOR N=375	95% CI
Fluoroquinolone resistance						
Susceptible	1		1		1	
Low-level resistance	2.9	0.8–10.5	34.1***	4.3–271.6	22.1**	2.4–207.5
High-level resistance	10.3***	3.1–35.0	83.9***	10.4–673.9	73.0***	7.8–679.2
Kanamycin resistance (vs susceptibility)	2.9	0.5–15.5	2.7	0.5–15.1	4.2	0.7–25.4
Isoniazid resistance (gDST)[a]	1.2	0.7–2.2	1.3	0.6–3.0	1.3	0.5–3.2
Isoniazid high-level resistance on gDST (vs other)	0.9	0.3–2.6	1.4	0.4–4.8	1.7	0.5–6.6
Ethambutol resistance (vs susceptibility)	1	0.5–1.9	1.7	0.5–5.7	1.6	0.4–5.9
Pyrazinamide resistance (vs susceptibility)	2.0*	1.1–3.8	2.6*	1.01–6.7	1.8	0.6–5.1
Ethionamide resistance (vs susceptibility)	1.2	0.6–2.4	2.2	0.8–6.0	3.6*	1.2–11.0
Sampling (targeted vs systematic)[b]	1.2	0.4–3.9	1.7	0.4–6.4	1.4	0.3–6.8
	N=81[c]		N=75[c]		N=68[c]	
Isoniazid resistance (pDST)[a]	1.9	0.7–5.0	2.3	0.8–6.5	3.6*	1.01–12.9
Isoniazid high-level resistance on pDST (vs other)	1.6	0.5–4.9	2.2	0.7–6.8	3.8*	1.03–13.7
Isoniazid resistance (gDST and pDST)[a]	1.8	0.7–4.8	2.3	0.8–6.5	3.6*	1.02–12.8
Isoniazid high-level resistance on gDST and pDST (vs other)	1.6	0.5–4.9	2.2	0.7–6.8	3.8*	1.03–13.7
	N=323[d]		NA[e]		NA[e]	
WHO STR eligibility in patients with FQ-/SLI-susceptible TB						
Eligible	1					
Resistance to a companion drug	1.01		0.4–2.8			

Odds ratios were adjusted for the sampling approach and level of initial resistance to fluoroquinolones.
aOR, adjusted odds ratio; CI, confidence interval; FL, failure; FQ, fluoroquinolone; gDST, genotypic drug susceptibility testing; INH, isoniazid; NA, not applicable; pDST, phenotypic drug susceptibility testing; RL, relapse; SLI, second-line injectable; STR, shorter multidrug-resistant tuberculosis treatment regimen.
* $p < 0.05$;
** $p < 0.01$;
*** $p < 0.001$.
[a] Odds for every increase between susceptibility, low-level resistance, moderate-level resistance, and high-level resistance.
[b] In addition to the systematic sample, patients with initial FQ resistance were sampled to enrich the cohort.
[c] Missing data: 329 patients for INH pDST and for INH gDST and pDST for success versus FL, RL, or died; 308 patients for INH pDST and for INH gDST and pDST for success versus FL or RL; 307 patients for INH pDST and for INH gDST and pDST for success versus FL.
[d] In patients with FQ-/SLI-susceptible tuberculosis, from systematic sample only; WHO eligible: no resistance to any of the STR components (except isoniazid) (WHO, 2019b).
[e] Regression data not shown: only one patient with treatment failure in 303 patients with initially FQ-susceptible tuberculosis.

Outcomes in patients with high-level fluoroquinolone resistance

Not considering those who died ($n = 7$), 34 (60.7%) of 56 patients with high-level fluoroquinolone resistance were cured, while 16 (28.6%) had treatment failure and 6 (10.7%) had relapse (Table 5). Among patients with high-level fluoroquinolone resistance, those with initial resistance to ethionamide were cured less likely than those with TB susceptible to ethionamide (35.7% vs 69.0%; aOR for having a bacteriologically unfavourable outcome: 3.8; 95% CI 1.1-12.9; $p = 0.03$).

In this small subgroup no patient had isoniazid-susceptible TB, and only one patient had low-level isoniazid-resistant TB. High-level isoniazid resistance (vs any other level) on pDST predicted treatment failure (8/15 (53.3%) vs 6/30 (20.0%); aOR 4.3; 95% CI 1.2-15.8; $p = 0.03$), with the same results for the combination of pDST and gDST.

Discussion

In this study, fluoroquinolone resistance and pyrazinamide resistance were associated with clinically adverse outcome (failure, relapse, or death) and bacteriologically adverse outcome (either failure or relapse) in patients treated with a standardized shorter MDR-TB treatment regimen. Moreover, success was less frequent when the level of isoniazid resistance was higher, and initial resistance to isoniazid was associated with treatment failure. Treatment failure but not relapse was also more likely in patients with initial resistance to ethionamide. In patients with initially fluoroquinolone-/second-line-injectable-susceptible TB, resistance to other drugs in the regimen (ethambutol, ethionamide, or pyrazinamide) was not associated with a clinically adverse outcome.

The association between fluoroquinolone resistance and adverse outcome with the shorter MDR-TB treatment regimen found in this study is in agreement with the findings of previous publications regarding the effectiveness of the regimen (Trébucq et al., 2019; Van Deun et al., 2019), although low-level resistance was not a predictor of failure in a prior analysis of a subset of the present cohort (Rigouts et al., 2016). This supports our understanding of later-generation fluoroquinolones as a core drug of the regimen having both high bactericidal activity and high sterilizing activity (Van Deun et al., 2018). Resistance to fluoroquinolones was not rare (24.4%; 118/483), albeit enriched in our cohort, and the proportion with high-level resistance has increased since the prior analysis. Hence, investments in rapid fluoroquinolone susceptibility testing seem justified. Detection of resistance to fluoroquinolones necessitates replacement by another drug with similar properties, with bedaquiline likely being the best candidate (Van Deun et al., 2018).

Every increase in level (susceptible, low-level resistance, moderate-level resistance, high-level resistance) of phenotypic isoniazid resistance increased the odds of treatment failure, which suggests that high-dose isoniazid continues to contribute to treatment success. These results are in line with findings of other studies (Frieden et al., 1996). A randomized controlled trial that compared high-dose isoniazid (16–18 mg/kg) with normal-dose isoniazid (5 mg/kg) and placebo for the treatment of MDR-TB found that high-dose isoniazid significantly decreased the time to smear conversion (Katiyar et al., 2008). In a study in which MDR-TB patients were treated with a partially standardized regimen, the

Table 5
Bacteriologically adverse outcome (either failure or relapse) among patients with high-level fluoroquinolone resistance by initial resistance to drugs included in the shorter treatment regimen.

	Total	Success		Failure		Relapse		p^b
	N	*N*	%	*N*	%	*N*	%	
	56	34	60.7	16	28.6	6	10.7	
KAN								0.7
S	52	32	61.5	14	26.9	6	11.5	
R	4	2	50.0	2	50.0	0	0	
INH (gDST)								0.5
S	2	2	100	0	0	0	0	
R low	3	1	33.3	2	66.7	0	0	
R moderate	42	27	64.3	10	23.8	5	11.9	
R high	9	4	44.4	4	44.4	1	11.1	
INH (pDST)[a]								0.1
S	0							
R low	1	1	100	0	0	0	0	
R moderate	34	23	67.6	6	17.6	5	14.7	
R high	16	7	43.8	8	50.0	1	6.3	
INH (gDST and pDST)[a]								0.1
S	0							
R low	1	1	100	0	0	0	0	
R moderate	34	23	67.6	6	17.6	5	14.7	
R high	16	7	43.8	8	50.0	1	6.3	
EMB								0.7
S	12	9	75.0	2	16.7	1	8.3	
R	44	25	56.8	14	31.8	5	11.4	
PZA								0.1
S	27	20	74.1	6	22.2	1	3.7	
R	29	14	48.3	10	34.5	5	17.2	
ETH								0.03
S	42	29	69.0	8	19.0	5	11.9	
R	14	5	35.7	8	57.1	1	7.1	

EMB, ethambutol; ETH, ethionamide; gDST, genotypic drug susceptibility testing; high, high level; INH, isoniazid; KAN, kanamycin; low, low level; moderate, moderate level; pDST, phenotypic drug susceptibility testing; PZA, pyrazinamide; R, resistant; S, susceptible.
[a] Data on level of phenotypic isoniazid resistance were missing for five patients.
[b] Fisher's exact test.

use of high-dose isoniazid (16–18 mg/kg) was associated with faster culture conversion and higher odds of successful outcome (Walsh et al., 2019). In the latter study, 94% of patients had high-level phenotypic isoniazid resistance, which was defined as resistance at 1.0 mg/L on 7H10 agar medium and corresponds to moderate-level or high-level resistance in our study. A recent study investigating the early bactericidal activity of isoniazid in isoniazid-resistant TB or MDR-TB found that high-dose isoniazid (10–15 mg/kg) is as effective for *inhA* mutants as normal-dose isoniazid (5 mg/kg) for isoniazid-susceptible TB (Dooley et al., 2020). In contrast, in a study that evaluated the countrywide implementation of the shorter MDR-TB treatment regimen in Niger, no association between the level of resistance to isoniazid and adverse treatment outcome was found (Piubello et al., 2020). This may be explained by the small numbers of patients with failure and relapse in that study, as well as the infrequent occurrence of double mutants of *inhA* and *katG*, affecting the power to detect an association.

Among patients with high-level fluoroquinolone resistance, treatment failure was more likely when patients had high-level isoniazid resistance (compared with moderate-level resistance among the vast majority of the remainder). These results suggest that even when high-dose gatifloxacin, a more powerful fluoroquinolone than moxifloxacin is used, high-dose isoniazid is a useful addition in virtually all patients treated with the shorter treatment regimen. Hence, testing for levels of isoniazid resistance (by pDST at a high concentration or by gDST) seems to have value for the constitution of an individualized regimen for fluoroquinolone-resistant MDR-TB.

In contrast to phenotypic resistance, genotypic resistance to isoniazid was not associated with adverse treatment outcome in our study, despite the previously described strong association between drug-resistance-conferring variants and phenotypic resistance levels (Lempens et al., 2018). The very low proportion of patients with isoniazid-susceptible TB may have affected the power to identify an association. Moreover, incomplete genotypic information for isoniazid resistance could have led to small numbers of false negatives. As more information on genotypic resistance patterns emerges through platforms such as ReSeqTB (Starks et al., 2015), we will be able to better explain these inconsistencies.

Bangladeshi people are mostly fast acetylators, which reduces their chance of experiencing adverse effects of isoniazid, in particular with high doses of the drug, compared with slow acetylators (Weber and Hein, 1979; Zaid et al., 2004). Evidence regarding the implementation of the shorter treatment regimen in countries with a larger proportion of slow acetylators shows, however, that adverse events were rare and manageable (Piubello et al., 2020; Trébucq et al., 2019).

We also found a correlation between initial pyrazinamide and ethionamide resistance and adverse treatment outcomes. However, for combination as a single category (any resistance to pyrazinamide, ethionamide, or ethambutol) we did not find a correlation with a clinically or bacteriologically adverse outcome. Treatment success was 93.3% among 242 patients according to WHO criteria not eligible due to resistance to pyrazinamide, ethionamide, or ethambutol, which is very similar to the 93.8% success among 81 eligible patients, and is much higher than the 73.7% success among 19 patients with initial resistance to fluoroquinolones. Hence, the present WHO guidelines (WHO, 2019b), which recommend the shorter treatment regimen not be used in patients with TB resistant to any of the components of the regimen (except isoniazid), may need to be revised, at least for a high-dose gatifloxacin-based regimen. To systematically test for pyrazinamide or ethionamide resistance would result in serious diagnostic delay, as their DST methods are not readily available in most high TB burden countries, for ethionamide DST is not very accurate, and gDST is still problematic, including interpretation of the numerous mutations. Given the high rate of treatment success among those with initial resistance to these drugs, the benefit gained would be questionable. Our findings are supported by other studies evaluating the shorter treatment regimen, some also using the weaker moxifloxacin at the standard dose (Piubello et al., 2020; Trébucq et al., 2019). We were unable to explore the role of second-line injectables, as initial resistance to kanamycin was very rare in this cohort. Moreover, no resistance to clofazimine was found (all isolates had the wild type *Rv0678* gene); hence, the effect of initial resistance to clofazimine could not be assessed.

A targeted sample of patients with fluoroquinolone resistance was included in this study to be able to identify the contribution of companion drugs when fluoroquinolones were no longer driving the regimen's efficacy. This, however, resulted in higher drug resistance frequencies and worse treatment outcomes than those in the general Damien Foundation Bangladesh MDR/RR-TB—population, and may thus limit the generalizability of our findings. Because of the retrospective design of our study, it was not possible to adapt sampling to the research question on the effect of initial resistance on outcome. For example, this led to relatively small groups of patients with low-level or high-level isoniazid resistance compared with moderate-level resistance. However, since we used programme data, our findings represent the reality of the setting. In addition, the Bangladesh dataset has undergone repeated rounds of data verification throughout the years, ensuring a clean and high-quality dataset.

In conclusion, our study confirms that gatifloxacin drives the efficacy of the shorter treatment regimen. Initial resistance to isoniazid, pyrazinamide, and ethionamide is associated with adverse outcomes; however, the effect on outcomes is not important enough to justify systematic baseline DST, especially when fluoroquinolone susceptibility is preserved. Hence, contrary to current guidelines (WHO, 2019b), exclusions to the regimen may thus be justified only in the case of fluoroquinolone or kanamycin resistance but not other drug resistance.

Declaration of interest

The authors declare that they have no competing interests.

Author contribution statement

BdJ, AVD, CM, and LR conceived and designed the study. PL, CM, KA, and MH acquired the data. TD and PL analysed and interpreted the data. PL and TD drafted the article. All authors revised the article critically and approved the submitted version.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.08.042.

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