Standardised shorter regimens *versus* individualised longer regimens for rifampin- or multidrug-resistant tuberculosis

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ABSTRACT We sought to compare the effectiveness of two World Health Organization (WHO)-recommended regimens for the treatment of rifampin- or multidrug-resistant (RR/MDR) tuberculosis (TB): a standardised regimen of 9–12 months (the "shorter regimen") and individualised regimens of ⩾20 months ("longer regimens").

We collected individual patient data from observational studies identified through systematic reviews and a public call for data. We included patients meeting WHO eligibility criteria for the shorter regimen: not previously treated with second-line drugs, and with fluoroquinolone- and second-line injectable agent-susceptible RR/MDR-TB. We used propensity score matched, mixed effects meta-regression to calculate adjusted odds ratios and adjusted risk differences (aRDs) for failure or relapse, death within 12 months of treatment initiation and loss to follow-up.

We included 2625 out of 3378 (77.7%) individuals from nine studies of shorter regimens and 2717 out of 13 104 (20.7%) individuals from 53 studies of longer regimens. Treatment success was higher with the shorter regimen than with longer regimens (pooled proportions 80.0% *versus* 75.3%), due to less loss to follow-up with the former (aRD −0.15, 95% CI −0.17−−0.12). The risk difference for failure or relapse was slightly higher with the shorter regimen overall (aRD 0.02, 95% CI 0–0.05) and greater in magnitude with baseline resistance to pyrazinamide (aRD 0.12, 95% CI 0.07–0.16), prothionamide/ethionamide (aRD 0.07, 95% CI −0.01–0.16) or ethambutol (aRD 0.09, 95% CI 0.04–0.13).

In patients meeting WHO criteria for its use, the standardised shorter regimen was associated with substantially less loss to follow-up during treatment compared with individualised longer regimens and with more failure or relapse in the presence of resistance to component medications. Our findings support the need to improve access to reliable drug susceptibility testing.

Introduction

Almost 600 000 individuals develop tuberculosis (TB) disease caused by rifampin- or multidrug-resistant (RR/MDR) strains of *Mycobacterium tuberculosis* every year [1]. Treatment of RR/MDR-TB is challenging and these patients have a substantial risk of unfavourable outcomes [1].

Since 2016, World Health Organization (WHO) guidelines have included the option of treating RR/MDR-TB with a standardised regimen of 9–12 months in duration (the "shorter regimen") instead of an individualised regimen of ⩾20 months ("longer regimens") [2]. Eligibility requirements for the shorter regimen include a high likelihood of susceptibility to fluoroquinolones and second-line injectable agents, and no previous treatment with second-line drugs. The shorter regimen is standardised; if any of its component drugs cannot be used then WHO recommends treatment with an individualised longer regimen. A number of uncertainties remain regarding these WHO recommendations.

First, the effectiveness of the shorter regimen compared with individualised longer regimens remains unclear. In a recently published randomised clinical trial comparing the shorter regimen with longer regimens composed per 2016 WHO guidelines, the shorter regimen was noninferior with respect to overall treatment success, but rates of nonconversion or reversion of cultures, relapse and death were higher in the shorter regimen arm [3, 4]. These associations were not statistically significant, albeit the trial was not powered for each outcome. Second, because the shorter regimen is standardised, whether it is effective in the face of resistance to its component medications has remained a matter of debate [5–10]. The WHO recommendation against use of the shorter regimen in the presence of resistance to any of its component medications has been questioned as being too restrictive [8, 11]. Third, it is unknown how the shorter regimen performs in comparison with longer regimens composed according to 2018 WHO guidelines that recommend bedaquiline and linezolid, and discourage the use of second-line injectable agents [12].

In recent years, individual patient data meta-analyses from observational studies have tried to answer key questions about the treatment of RR/MDR-TB [13–15]. Considered the "gold standard" method for bringing together data from different studies, individual patient data meta-analysis includes a number of advantages over aggregate data meta-analysis. These include verification of data, standardisation of outcomes, use of multivariable analyses to adjust for potential confounding by other covariates and use of propensity score-based analyses to address potential confounding by indication [16, 17]. We applied this methodology to compare standardised shorter regimens to individualised regimens of longer duration.

Methods

Objectives

We sought to compare the effectiveness of standardised shorter regimens to regimens of longer duration, composed following WHO guidelines for the treatment of RR/MDR-TB.

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Regimen definitions

We defined shorter regimens as standardised regimens with an intended duration of 9–12 months including 4–6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, ethambutol and high-dose isoniazid, followed by 5–8 months of moxifloxacin, clofazimine, pyrazinamide, ethambutol and, optionally, prothionamide [2]. The following within-class drug substitutions were permitted: gatifloxacin or levofloxacin instead of moxifloxacin, ethionamide instead of prothionamide, amikacin or capreomycin instead of kanamycin and usual-dose isoniazid instead of high-dose isoniazid.

We defined longer regimens per 2016 WHO guidelines as individualised regimens that included a later-generation fluoroquinolone and a second-line injectable among at least five anti-TB medications considered to be effective based on drug susceptibility testing (DST) or at least four anti-TB medications considered effective plus pyrazinamide [2]. We counted bedaquiline, linezolid, carbapenems and delamanid as effective medications [15, 18]. As WHO guidelines permit flexibility around the total recommended duration of 20 months [12], we used 18 months of treatment as the minimum total duration for a longer regimen.

In December 2018, WHO issued new guidelines for the composition of longer regimens. As such, we undertook an analysis (initially unplanned) to compare contemporary shorter and longer regimens. For this, we restricted shorter regimens to those using either moxifloxacin or levofloxacin (as gatifloxacin is no longer available) and we restricted longer regimens to those whose composition met 2018 WHO guidelines by using at least three drugs from group A (moxifloxacin/levofloxacin, bedaquiline, linezolid) plus at least one drug from group B (cycloserine/terizidone, clofazimine) or at least two drugs from each group, and not including kanamycin or capreomycin.

Study selection, quality assessment and data management

We identified studies from two previously published systematic reviews: one of shorter regimens [13] and one restricted to other regimens [15, 19]. Search and selection criteria have been previously reported [13, 15, 19]. Briefly, we reviewed medical databases to identify studies of RR/MDR-TB treatment published from January 2009 to September 2015; the search was updated in April 2016. To be eligible, studies had to have reported end-of-treatment outcomes for at least 25 patients with bacteriologically confirmed RR/MDR-TB, with clear descriptions of treatment regimens [13, 15, 19]. In this update, investigators of previously identified studies provided data on additional patients from their centres and we also added unpublished data that WHO had obtained through a public call for datasets issued in February 2018 [20]. We assessed study quality using a checklist of seven indicators adapted from the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool and classified studies into high, moderate or low quality [15, 21].

Investigators provided de-identified individual patient-level data on clinical variables (age, sex, HIV status, previous treatment with first- or second-line anti-TB drugs), methods and dates of TB diagnosis and DST, indicators of disease severity (results of sputum acid-fast bacilli microscopy, presence of cavities or bilateral involvement on chest radiographs), treatment regimen composition (including dose and duration for each drug), and end-of-treatment outcomes. We verified data with investigators, created variables common to all datasets and then concatenated the data to create two individual patient datasets: one for shorter regimens and one for longer regimens.

Treatment outcomes

Studies reported outcomes of cure, treatment completion, failure, loss to follow-up, death during treatment and relapse [13, 15]. When defining these outcomes, the majority of longer regimen studies used 2008 or 2013 WHO definitions [22, 23] and shorter regimen studies used similar definitions adapted to a treatment duration of 9–12 months (supplementary table A1). For analysis, we combined outcomes of cure and treatment completion into a single outcome of treatment success. When studies provided data to distinguish re-infection and relapse, we only counted occurrences of the latter.

Patient selection

We included patients with RR/MDR-TB confirmed either by culture or molecular DST methods and meeting WHO criteria for use of the shorter standardised regimen: no previous treatment with second-line drugs and not infected with *M. tuberculosis* resistant to fluoroquinolones or second-line injectable agents (excluded by DST or considered unlikely). Patients with TB resistant to second-line injectable agents were included if treated with an alternative drug of the same class. We excluded individuals with DST-confirmed isoniazid-susceptible TB (*i.e.* the RR group consisted of individuals in whom DST to isoniazid had not been performed).

From both longer and shorter regimen groups, we excluded patients who were not treated per WHO guidelines. Because WHO recommends the shorter regimen as standardised, we excluded patients in whom DST results had been used to alter the regimen's composition. From the longer regimen group, we excluded patients who did not receive a later-generation fluoroquinolone and a second-line injectable agent, and those treated with fewer than five effective drugs or with pyrazinamide and fewer than four effective drugs. We counted medications as effective if susceptibility was confirmed by DST, with the exception of cycloserine, clofazimine and linezolid, which we assumed effective in the absence of confirmed resistance, and bedaquiline, carbapenems and delamanid, which we always counted as effective. From both shorter and longer regimen groups, we excluded patients who had been assigned a successful treatment outcome but were treated for less than the minimal recommended duration (we used 8 and 17.5 months, respectively, as cut-offs for minimal duration). From the shorter regimen group, we excluded patients whose treatment was prolonged for >1 month beyond what their programme had reported as the maximum duration of shorter treatment; such exclusions did not apply to longer regimens because there is no recommended upper limit of treatment duration. We excluded patients with missing outcomes. Our mortality outcome was death during treatment, which meant that the likelihood of death being observed would be higher with lengthier durations of treatment. To avoid bias from this differential ascertainment, we excluded participants who died 12 months after starting therapy.

Data analysis

In all multivariable analyses, we adjusted for the following covariates that were considered important potential confounders: age, sex, HIV status, prior treatment with first-line anti-TB drugs and extensiveness of TB disease. We classified disease as extensive if sputum was smear positive or, when smear results were missing, if chest radiography demonstrated cavities. If cavitation was not reported, we classified disease as extensive if there were bilateral abnormalities on chest radiography.

We first calculated pooled percentages of each treatment outcome for shorter and longer regimens using random effects aggregate data meta-analyses with the exact binomial likelihood method [24]. Heterogeneity was estimated using the I^2 statistic. We then performed one-step individual patient-level data meta-analyses using generalised logistic mixed effects meta-regression to estimate adjusted odds ratios (aORs) (random intercept for matched pairs and fixed slope) and adjusted risk differences (aRDs) (fixed intercept and slope) with 95% confidence intervals for the following outcomes: 1) failure or relapse *versus* success, 2) death *versus* success and 3) loss to follow-up *versus* success, failure or relapse. Estimates were calculated overall (including all patients) and within pre-specified subgroups, defined by HIV status, disease extensiveness, and baseline DST results for pyrazinamide, prothionamide/ethionamide and ethambutol. For analyses stratified by DST to these drugs, we excluded patients in whom fluoroquinolone susceptibility had been assumed rather than confirmed. We conducted two sensitivity analyses. In the first, we included patients with isoniazid-susceptible RR-TB. In the second, we compared the two regimens for the treatment of fluoroquinolone-resistant RR/MDR-TB.

We interpreted associations based on aORs rather than risk differences, as the former were estimated with random effects. Rather than using p-value-based decisions about statistical significance [25], we used the bounds of the 95% confidence intervals to determine if an association was potentially important. We considered a positive association (*i.e.* with OR point estimate >1) as important if the lower bound of the 95% confidence interval was >0.95 and a negative association (*i.e.* with OR point estimate <1) as important if the upper bound of the 95% confidence interval was <1.05 [25]. While we reported both aORs and aRDs in tables, in the text we refer to aRDs because risks are more intuitive to understand than odds.

In all analyses, adjustment was done using propensity scores that we calculated using the potential confounders. We matched shorter and longer regimen treated patients 1:1 with replacement [16], *via* the calliper method with difference of 0.02 allowed, and exact matching on HIV status. We imputed missing data with the method of multivariate imputation by chained equations for use in the adjusted analyses [26]. For calculating propensity scores, we imputed missing values for age, HIV status, prior use of first-line drugs and extensiveness of disease. We imputed DST for the purposes of counting the number of effective medications. We did not use imputed covariates or DST to select patients for subgroup analyses (*e.g.* if stratifying analyses by pyrazinamide resistance, we excluded patients without pyrazinamide DST). We generated 20 datasets that included measured and imputed values, performed multivariable analyses in each one, and then pooled the results using Rubin's rules to calculate adjusted effect estimates [26–28].

Meta-analyses and imputation were performed using the statistical software R with the packages metafor version 2.0-0, lme4 version 1.1-21 and mice version 3.4.0 [29, 30]. The protocol can be obtained by contacting the corresponding author.

Results

Study and patient selection

We identified six studies of shorter regimens and 43 studies of longer regimens from previously published systematic reviews [13, 15, 19], to which we added 13 studies (three shorter and 10 longer) identified through the WHO public call (supplementary figure A1). Individual-level data were available for 3378 patients treated with shorter regimens and 13 104 patients treated with longer regimens. No important issues were identified in checking the individual patient data.

Table 1 enumerates the reasons why we excluded 753 out of 3378 (22%) individuals treated with shorter regimens and 10 387 out of 13 104 (79%) individuals treated with longer regimens. Of those excluded from the longer regimens, 5012 out of 10 387 (48%) were excluded because they did not meet WHO criteria for eligibility for shorter regimen treatment. Exclusions due to regimens whose composition did not follow WHO guidelines were more common in the longer regimen group, whereas exclusions due to treatment durations not meeting recommendations were more common in the shorter regimen group. The proportion of individuals excluded due to missing data on duration or outcomes was higher in the longer regimen group. In both groups, the proportion excluded due to deaths occurring after month 12 of treatment was small (<1%). Overall, we included 2625 out of 3378 (77.7%) individuals from nine studies

TABLE 1 Selection of patients from individual patient databases

	Shorter	Longer
Patients in initial database	3378	13 104
Reasons for exclusion		
Did not meet WHO criteria for standardised shorter regimens	306	5012
Rifampin resistance not confirmed	115	11
Previous treatment with second-line TB drugs	33	2301
XDR-TB	10	1912
Fluoroquinolone-resistant TB (excluding XDR)	137	1149
Second-line injectable-resistant TB (excluding XDR)	22	1222
Did not meet criteria for inclusion in individual patient data meta-analyses	447	5375
Isoniazid-susceptible TB	210	15
Not treated with a shorter regimen[#]	151	NA
Not treated with later-generation fluoroquinolone	NA	2954
Not treated with second-line injectable	NA	917
Other	23	0
Duration or outcome data missing	52	1852
Not treated with $\geqslant$4 effective drugs and pyrazinamide or $\geqslant$5 effective drugs[¶]	NA	775
Successful outcome reported, but with less than minimum recommended duration, or any outcome beyond maximum duration[+]	52	154
Died after month 12 of treatment[§]	2	121
Included in main analyses	2625	2717

Data are presented as n. Individuals with more than one exclusion criteria are included in the counts for each applicable criterion, such that the sum of the exclusion criteria counts is greater than the total number of patients excluded. WHO: World Health Organization; TB: tuberculosis; XDR: extensively drug-resistant; NA: not applicable. [#]: we also excluded patients treated with standardised shorter treatment regimens modified to include a drug from a class outside of the usual composition (*e.g. para*-aminosalicylic acid, cycloserine/terizidone, bedaquiline). [¶]: among those otherwise meeting criteria for inclusion. [+]: we excluded patients in whom a successful outcome was recorded if their treatment duration was <8 months with a shorter regimen or <17.5 months with a longer regimen. Patients on shorter regimens were excluded regardless of their outcome if treatment lasted 1 month beyond the upper limit of the maximum duration of treatment with the shorter regimen. [§]: among those otherwise meeting criteria for inclusion. See Methods for rationale.

TABLE 2 Clinical characteristics of included patients

	Shorter	Longer
Patients	2625	2717
Age years	35.4±13.0	36.6±12.4
Children and adolescents (age <16 years)	53 (2.0)	29 (1.1)
Male	1682 (64.1)	1590 (58.5)
People living with HIV	380 (14.5)	1156 (42.8)
Antiretroviral therapy	328 (86.3)	1077 (93.2)
Acid-fast bacilli smear positive	2224 (88.6)	1820 (69.4)
Cavitation on chest radiography	501 (40.1)	465 (52.2)
Bilateral disease on chest radiography	1617 (88.6)	409 (61.6)
Extensive disease[#]	2256 (88.2)	1873 (69.1)
Previous treatment with first-line drugs	2209 (87.7)	1355 (50.3)
High-income country	0 (0.0)	562 (20.7)
Upper-middle-income country	41 (1.6)	1704 (62.7)
Low-middle- or low-income country	2584 (98.4)	451 (16.6)
Pyrazinamide		
Resistant	317 (52)	440 (44.3)
Sensitive	293 (48)	554 (55.7)
No data (% of all)	2015 (76.8)	1723 (63.4)
Ethambutol		
Resistant	843 (63.9)	723 (62.5)
Sensitive	477 (36.1)	434 (37.5)
No data (% of all)	1305 (49.7)	1560 (57.4)
Ethionamide/prothionamide		
Resistant	291 (26.8)	200 (20.5)
Sensitive	795 (73.2)	777 (79.5)
No data (% of all)	1539 (58.6)	1740 (64.0)
Clofazimine		
Resistance	0	4 (5.3)
Sensitive	8 (100)	71 (94.7)
No data (% of all)	2617 (99.7)	2642 (97.2)
***Para*-aminosalicylic acid**		
Resistance	10 (1.5)	57 (7.0)
Sensitive	662 (98.5)	756 (93.0)
No data (% of all)	1953 (74.4)	1904 (70.1)
Cycloserine/terizidone		
Resistance		16 (2.8)
Sensitive		549 (97.2)
No data (% of all)	2625 (100)	2152 (79.2)
Linezolid		
Resistance		2 (1)
Sensitive		190 (99)
No data (% of all)	2625 (100)	2525 (92.9)

Data are presented as n, mean±SD or n (%), unless otherwise stated. [#]: patients were classified as having extensive disease if they were smear positive and as having disease that was not extensive if their sputum was smear negative; in those missing data on smear status, their disease was classified as extensive if chest radiographs demonstrated cavitation and not extensive in the absence of cavitation. In studies where cavitation was not reported, disease was classified as extensive if there were bilateral chest radiographic abnormalities and not extensive in the absence of bilateral involvement.

([7, 31–34] and unpublished data as indicated in the supplementary material) of shorter regimens and 2717 out of 13 104 (20.7%) individuals from 39 studies of longer regimens ([35–65] and unpublished data as indicated in the supplementary material). Of the 48 included studies, 39 (81%) were of high quality, eight (17%) were of moderate quality and one (2%) was of low quality (supplementary table A2).

Description of included patients and regimens

Table 2 summarises patient characteristics and DST results. Distributions of age and sex were similar between the two groups. Patients treated with longer regimens were more likely to be people living with HIV and to have cavitary TB. Those treated with the shorter regimen were more likely to have smear-positive TB, bilateral disease, previous treatment with first-line drugs and been treated in

TABLE 3 Regimen composition of shorter and longer regimens included in analyses

	Shorter	Longer
Patients in analysis	2625	2717
Drug used		
Pyrazinamide	2625 (100)	2444 (90)
Ethambutol	2625 (100)	1325 (48.8)
High-dose isoniazid	2442 (93)	439 (16.2)
Moxifloxacin	1378 (52.5)	2131 (78.4)
Gatifloxacin	1040 (39.6)	2 (0.1)
Levofloxacin	207 (7.9)	716 (26.4)
Amikacin	21 (0.8)	366 (13.5)
Kanamycin	2471 (94.1)	2032 (74.8)
Capreomycin	135 (5.1)	476 (17.5)
Prothionamide/ethionamide	2625 (100)	2470 (90.9)
Clofazimine	2625 (100)	167 (6.1)
Linezolid	0	244 (9.0)
Para-aminosalicylic acid	0	825 (30.4)
Cycloserine	0	901 (33.2)
Bedaquiline	0	320 (11.8)
Carbapenems	0	21 (0.7)
Delamanid	0	16 (0.6)
Duration of intensive phase months[#]	4 (3.9–4.0)	7.8 (6.1–9.1)
Duration of treatment months[#]	9 (8.9–9.7)	21.6 (19.5–24.0)

Data are presented as n, n (%) or median (interquartile range). [#]: among successfully treated patients.

low-middle- or low-income countries (98.4% *versus* 16.6%). Numbers of people living with HIV not on antiretroviral therapy were small in both groups. Prevalence of resistance to pyrazinamide, prothionamide/ethionamide and ethambutol was similar between the two groups. Resistance to pyrazinamide, ethambutol and prothionamide/ethionamide was correlated (supplementary table A3). Few patients had DST for clofazimine, *para*-aminosalicylic acid, cycloserine and linezolid.

Regimen composition is summarised in table 3. Moxifloxacin was the most common fluoroquinolone in both regimens. Only two out of 2717 (0.1%) patients treated with longer regimens received gatifloxacin *versus* 1040 out of 2625 (39.6%) patients treated with the shorter regimen. Kanamycin was the most common second-line injectable used. Less than half the patients treated with longer regimens received isoniazid, ethambutol and clofazimine *versus* all patients treated with the shorter regimen. In the longer regimen group, bedaquiline was used in 320 out of 2717 (11.8%) patients, linezolid in 244 out of 2717 (9.0%) patients, a carbapenem in 21 out of 2717 (0.7%) patients and delamanid in 16 out of 2717 (0.6%) patients.

Aggregate data meta-analyses
The pooled rate of treatment success was higher with the shorter regimen (80.0%) compared with longer regimens (75.3%) (table 4). Fewer patients treated with the shorter regimen were lost to follow-up (shorter 4.2% *versus* longer 14.6%) and more experienced failure or relapse (shorter 3.6% *versus* longer 2.7%) and death (shorter 7.6% *versus* longer 4.6%). Heterogeneity was high for each outcome, for both regimens. Forest plots are given in supplementary figures A2–A4.

Individual patient data meta-analyses
In univariable analyses (supplementary table A4), failure or relapse was positively associated with extensive disease, ethambutol resistance and pyrazinamide resistance. Death was positively associated with age, HIV status and prior treatment with first-line drugs. Loss to follow-up was positively associated with male sex and prior treatment with first-line drugs, and negatively associated with pyrazinamide resistance.

In multivariable analyses, there was an association between treatment with the shorter regimen and higher odds and risks of failure or relapse that was borderline overall (table 5), but important in subgroups where there was baseline resistance to pyrazinamide (aRD 0.12, 95% CI 0.07–0.16), prothionamide/ethionamide (aRD 0.07, 95% CI −0.01–0.16) and ethambutol (aRD 0.09, 95% CI 0.04–0.13). In the presence of resistance to at least two of these medications, the shorter regimen was also associated with greater failure or relapse (aRD 0.10, 95% CI 0.05–0.15) (supplementary table A5). Death during the first 12 months of

TABLE 4 Pooled percentage of treatment outcomes from aggregate data meta-analysis

	Success	Failure or relapse	Death during first 12 months of treatment	Loss to follow-up
Shorter (9 studies)	2164/2625 80.0% (72.1–86.1%)	118/2625 3.6% (1.3–9.6%)	201/2625 7.6% (4.2–13.1%)	142/2625 4.2% (2.3–7.5%)
Heterogeneity estimates	I^2=92%, τ^2=0.35	I^2=95%, τ^2=2.04	I^2=91%, τ^2=0.60	I^2=85%, τ^2=0.51
Longer (39 studies)	1814/2717 75.3% (69.8–80.0%)	112/2717 2.7% (1.5–4.7%)	265/2717 4.6% (2.9–7.2%)	526/2717 14.6% (11.0–19.0%)
Heterogeneity estimates	I^2=79%, τ^2=0.42	I^2=60%, τ^2=0.80	I^2=69%, τ^2=0.74	I^2=76%, τ^2=0.50

treatment was not associated with regimen type (table 6). Risks of loss to follow-up were lower with the shorter regimen, overall (aRD −0.15, 95% CI −0.17−−0.12) and in most subgroups (table 7).

A total of 1166 patients were included in the secondary analysis comparing moxifloxacin- or levofloxacin-containing shorter regimens (n=1004) with longer regimens composed per 2018 WHO recommendations (n=162). As shown in supplementary table A6, the groups had similar distributions of age, sex and extensive disease. HIV infection was less common in the shorter regimen group (shorter 20.4% *versus* longer 57.4%) and previous first-line treatment was more common (shorter 82.5% *versus* longer 45.9%). Of patients treated with shorter regimens, 96% resided in low- or low-middle-income countries, whereas 92% of those treated with longer regimens resided in upper-middle-income countries. Resistance to pyrazinamide, ethambutol or prothionamide/ethionamide was each more common in the longer regimen group (pyrazinamide: shorter 59% *versus* longer 77.3%; ethambutol: shorter 67.6% *versus* longer 78.3%; prothionamide/ethionamide: shorter 50.2% *versus* longer 61.9%). As shown in table 8, moxifloxacin- or levofloxacin-based shorter regimens were associated with greater risk of death compared with longer regimens constructed per 2018 WHO guidelines, although confidence intervals included the null value (aOR 2.5, 95% CI 1.0–6.3; aRD 0.11, 95% CI −0.01–0.22). There were no important differences in failure or relapse and loss to follow-up.

Sensitivity analyses

When patients with isoniazid-susceptible RR-TB were included (supplementary table A7a), failure or relapse was not associated with type of regimen, but death was weakly associated with the shorter regimen

TABLE 5 Comparison of shorter regimens and individualised longer regimens for outcome of failure or relapse *versus* success, using propensity score matched individual patient data meta-analysis

	Studies shorter:longer	Shorter events/total	Longer events/total	Propensity score matched multivariable meta-regression		
				Pairs	aOR (95% CI)	aRD (95% CI)
Overall	9:38	118/2282	112/1926	1926	2.0 (0.96–4.0)[+]	0.02 (0.00–0.05)[+]
HIV status strata						
People living with HIV	5:10	24/295	55/750	295	2.1 (0.6–7.7)	0.03 (−0.02–0.07)
HIV negative	9:38	94/1978	56/1162	1162	1.9 (0.9–4.0)	0.02 (−0.00–0.04)
Extensiveness						
Extensive	9:36	91/1969	83/1320	1320	1.2 (0.6–2.6)	0.01 (−0.02–0.03)
Not extensive	8:26	20/259	28/602	259	2.9 (0.8–10)	0.05 (0.00–0.09)
Pyrazinamide DST[#]						
Resistant	5:26	36/270	11/349	270	10.7 (1.8–64.5)[¶,+]	0.12 (0.07–0.16)[+]
Susceptible	5:23	12/248	13/428	248	1.3 (0.3–6.7)	0.01 (−0.04–0.05)
Ethionamide/prothionamide DST[#]						
Resistant	5:26	23/249	4/149	149	3.9 (1.0–15.1)[¶,+]	0.07 (−0.01–0.16)[+]
Susceptible	4:30	7/660	26/613	613	0.1 (0.0–1.5)	−0.03 (−0.05−−0.01)
Ethambutol DST[#]						
Resistant	8:37	39/692	27/554	554	3.1 (1.8–5.3)[¶,+]	0.09 (0.04–0.13)[+]
Susceptible	3:23	1/297	9/334	297	0.2 (0.0–1.9)	−0.02 (−0.04–0.01)

Data are presented as n, unless otherwise stated. aOR: adjusted odds ratio; aRD: adjusted risk difference; DST: drug susceptibility testing. All models adjusted for age, sex, HIV status, previous treatment with first-line tuberculosis medications and extensiveness of disease. Results were adjusted as described in the Methods. [#]: analyses restricted to patients with DST-confirmed fluoroquinolone susceptibility (*i.e.* excluding those with no DST data for fluoroquinolones); [¶]: aOR calculated from fixed effect model; [+]: confidence intervals suggestive of increased odds or risk of failure or relapse with the shorter regimen.

TABLE 6 Comparison of shorter regimens and individualised longer regimens for outcome of death during the first 12 months of treatment *versus* success, using propensity score matched individual patient data meta-analysis

	Studies shorter:longer	Shorter events/total	Longer events/total	Propensity score matched multivariable meta-regression		
				Pairs	aOR (95% CI)	aRD (95% CI)
Overall	9:37	201/2365	265/2079	2079	1.2 (0.95–1.6)	0.02 (−0.01–0.05)
HIV status strata						
People living with HIV	5:9	72/343	169/864	343	1.0 (0.6–1.6)	0.00 (−0.08–0.08)
HIV negative	9:37	127/2011	96/1202	1202	0.8 (0.4–1.4)	−0.01 (−0.04–0.01)
Extensiveness strata						
Extensive	9:35	165/2043	185/1422	1422	1.0 (0.8–1.3)	0.00 (−0.03–0.03)
Not extensive	8:28	27/266	79/653	266	1.6 (0.5–5.6)	0.02 (−0.04–0.07)
Pyrazinamide DST[#]						
Resistant	5:27	16/250	33/371	250	0.3 (0.1–1.4)	−0.05 (−0.11–0.02)
Susceptible	4:23	19/255	19/434	255	1.4 (0.4–5.5)	0.01 (−0.05–0.07)
Ethionamide/prothionamide DST[#]						
Resistant	4:26	18/244	9/154	154	1.5 (0.3–7.4)	0.02 (−0.05–0.08)
Susceptible	4:30	61/714	36/623	623	2.1 (0.8–5.8)	0.02 (−0.01–0.06)
Ethambutol DST[#]						
Resistant	8:36	58/711	44/571	554	0.6 (0.2–2.2)	−0.01 (−0.05–0.02)
Susceptible	3:23	22/318	18/343	318	2.4 (0.3–23.6)	0.03 (−0.01–0.07)

Data are presented as n, unless otherwise stated. aOR: adjusted odds ratio; aRD: adjusted risk difference; DST: drug susceptibility testing. All models adjusted for age, sex, HIV status, previous treatment with first-line tuberculosis medications and extensiveness of disease. Results were adjusted as described in the Methods. [#]: analyses restricted to patients with DST-confirmed fluoroquinolone susceptibility (*i.e.* excluding those with no DST data for fluoroquinolones).

(aOR 1.2, 95% CI 0.96–1.5; aRD 0.02, 95% CI −0.01–0.05). For RR/MDR-TB additionally resistant to fluoroquinolones, treatment with the shorter regimen was associated with increased failure or relapse (aOR 15.0, 95% CI 2.8–80.6; aRD 0.33, 95% CI 0.22–0.44) (supplementary table A7b).

TABLE 7 Comparison of shorter regimens and individualised longer regimens for outcome of loss to follow-up *versus* success, using propensity score matched individual patient data meta-analysis

	Studies shorter:longer	Shorter events/total	Longer events/total	Propensity score matched multivariable meta-regression		
				Pairs	aOR (95% CI)	aRD (95% CI)
Overall	9:37	142/2424	526/2452	2424	0.2 (0.2–0.3)[§]	−0.15 (−0.17−−0.12)[§]
HIV status strata						
People living with HIV	5:10	13/308	237/987	308	0.1 (0.1–0.3)[§]	−0.20 (−0.28−−0.13)[§]
HIV negative	9:38	129/2107	286/1448	1448	0.3 (0.2–0.4)[§]	−0.13 (−0.15−−0.10)[§]
Extensiveness strata						
Extensive	9:37	122/2091	368/1688	1688	0.3 (0.2–0.4)[§]	−0.15 (−0.18−−0.12)[§]
Not extensive	8:27	16/275	157/759	275	0.3 (0.1–0.5)[§]	−0.13 (−0.20−−0.06)[§]
Pyrazinamide DST[#]						
Resistant	5:28	13/283	54/403	283	0.2 (0.0–1.4)	−0.10 (−0.16−−0.04)
Susceptible	5:25	17/265	103/531	265	0.3 (0.1–0.5)[§]	−0.15 (−0.22−−0.07)[§]
Ethionamide/prothionamide DST[#]						
Resistant	5:27	13/262	42/191	191	0.1 (0.0–0.4)[§]	−0.19 (−0.26−−0.12)[§]
Susceptible	4:28	53/713	122/735	713	0.4 (0.3–0.7)[§]	−0.07 (−0.11−−0.04)[§]
Ethambutol DST[#]						
Resistant	8:38	47/739	113/667	667	0.3 (0.0–2.2)	−0.10 (−0.14−−0.06)
Susceptible	3:24	25/322	72/406	322	0.4 (0.2–0.7)[§]	−0.11 (−0.19−−0.04)[§]

Data are presented as n, unless otherwise stated. aOR: adjusted odds ratio; aRD: adjusted risk difference; DST: drug susceptibility testing. All models adjusted for age, sex, HIV status, previous treatment with first-line tuberculosis medications and extensiveness of disease. Results were adjusted as described in the Methods. [#]: analyses restricted to patients with DST-confirmed fluoroquinolone susceptibility (*i.e.* excluding those with no DST data for fluoroquinolones); [§]: confidence intervals suggestive of lower odds or risk of loss to follow-up with the shorter regimen.

TABLE 8 Comparison of moxifloxacin- or levofloxacin-based shorter regimens to longer regimens meeting WHO 2018 composition and duration criteria, using propensity score matched individual patient data meta-analysis, among patients with rifampin- or multidrug-resistant tuberculosis (TB) confirmed susceptible to fluoroquinolones

	Studies shorter:longer	Shorter events/total	Longer events/total	Propensity score matched multivariable meta-regression		
				Pairs	aOR (95% CI)	aRD (95% CI)
Failure or relapse *versus* success	9:10	81/881	10/135	135	1.4 (0.5–4.1)	0.03 (−0.05–0.11)
Death during first 12 months of treatment *versus* success	9:9	79/879	13/138	138	2.5 (1.0–6.3)[+]	0.11 (−0.01–0.22)
Lost *versus* success, failure or relapse	9:10	44/925	14/149	149	0.6 (0.1–4.5)	−0.01 (−0.09–0.07)

Data are presented as n, unless otherwise stated. aOR: adjusted odds ratio; aRD: adjusted risk difference. All models adjusted for age, sex, HIV status, previous treatment with first-line TB medications and extensiveness of disease. Results were adjusted as described in the Methods. [+]: confidence intervals suggestive of increased odds or risk of death with the shorter regimen.

Discussion

In this individual patient-level data meta-analysis on the treatment of RR/MDR-TB without documented resistance to fluoroquinolones or second-line injectables, we found the unadjusted pooled rate of treatment success was higher with the standardised shorter regimen compared with individualised longer regimens composed per 2016 WHO guidelines. In adjusted analyses, we observed the standardised shorter regimen was associated with a higher risk of bacteriological failure or relapse, notably in the presence of resistance to pyrazinamide, prothionamide/ethionamide and ethambutol. We also observed that the adjusted risk of loss to follow-up while on treatment was lower among patients treated with the standardised shorter regimen, a finding consistent in multiple subgroup and sensitivity analyses. We did not identify significant associations between regimen and risk of death in our pre-specified analyses. A *post hoc* subgroup analysis comparing longer regimens that followed 2018 WHO guidelines (including bedaquiline and/or linezolid) with contemporary shorter regimens (that used either moxifloxacin or levofloxacin) found risk of death was significantly higher in the latter group.

Our findings are consistent with results of the STREAM study, the recently published randomised clinical trial that showed the noninferiority of the shorter regimen *versus* longer standardised regimens, for a composite end-point of bacteriological outcomes, death and treatment completion [3, 4]. In STREAM, the proportion not completing treatment per protocol was higher with the longer regimens (30.3% *versus* 6.7%), there was a nonsignificant increase of unfavourable microbiological outcomes with the shorter regimen (relative risk of sputum culture nonconversion or reversion of 2.4, 95% CI 0.85–7.0) [4] and, in the per protocol analysis, an unfavourable outcome was more likely with the shorter regimen in the presence of pyrazinamide resistance.

The findings from our study add to a growing body of evidence in support of increasing access to reliable and reproducible DST for all patients with RR/MDR-TB [66, 67]. In a number of our analyses, resistance was associated with greater failure or relapse with the shorter regimen: for pyrazinamide, ethambutol, prothionamide/ethionamide as well as resistance to fluoroquinolones (assessed in a sensitivity analysis). However, there remains controversy about the clinical relevance of these findings [68–70], including among the authors of this study. This is because the association of failure or relapse with resistance to pyrazinamide, ethambutol or prothionamide/ethionamide in the treatment of RR/MDR-TB was not significant in some studies [7, 31], and because concerns exist about the accuracy of DST to ethambutol and prothionamide/ethionamide [70–72].

Our study has a number of limitations. First, there is the possibility of bias from residual confounding, particularly because the majority of shorter regimen data originated from low- or low-middle-income countries (98.4%) and the majority of longer regimen data originated from high- or upper-middle-income countries (83.4%). Programmes in the latter settings are likely to have had greater resources, including for the management of comorbidities such as HIV, which would be expected to contribute to better outcomes. Second, it is possible that differences in the definition of treatment failure between longer and shorter regimen studies contributed to the observation of less failure with the former; however, our findings on failure and relapse were similar to those of STREAM where uniform outcome definitions were used. Third, the data available did not permit a comparison between shorter and longer regimen studies with respect to adverse events, due to important differences in ascertainment. However, in STREAM the frequency of grade ⩾3 adverse events was similar in the two arms (45.4% and 48.2% for longer and shorter regimens, respectively) [3]. A recent meta-analysis restricted to longer regimens reported that risks of adverse events

were low for bedaquiline, clofazimine and fluoroquinolones, and high for second-line injectables and linezolid [73]. Fourth, because we did not apply an upper limit to duration when defining longer regimens, it is possible that success rates with these regimens were underestimated due to confounding by indication for prolonged treatment. Fifth, because some patients lost to follow-up during treatment may have been undiagnosed failure cases, it is possible that failure or relapse was less likely to be detected in the longer regimens. Finally, caution is warranted in interpretation of differences in loss to follow-up as noncompletion of treatment with a shorter regimen may carry a greater risk of death or failure than noncompletion of a longer regimen. This was suggested in the STREAM trial, where even participants that did not complete treatment were followed, such that outcomes through 104 weeks of follow-up were known for 95% of those treated with the longer regimens and 99% of those treated with the shorter regimen. In that trial, excess deaths were observed in the latter group after week 76 of follow-up.

The study also has a number of strengths. First, the amount and quality of data, from a diversity of settings, has improved the generalisability and strengthened the evidence base for the shorter regimen. Second, individual-level data enabled us to reduce selection and confounding bias that could not have been addressed through aggregate meta-analysis. Third, we were able to contribute to the ongoing debate about the effectiveness of the standardised shorter regimen in the presence of resistance to component medications, something that was not fully addressed by the STREAM trial. Finally, we were able to compare the shorter regimen to longer regimens that follow 2018 WHO guidelines, an endeavour that would require a number of years if undertaken prospectively. However, our results should be interpreted with caution because this comparison was initially unplanned and based on a small subgroup.

Conclusions

Compared with individualised longer regimens for the treatment of RR/MDR-TB susceptible to fluoroquinolones and second-line injectables, the standardised shorter regimen is associated with less loss to follow-up. In the presence of resistance to pyrazinamide, ethambutol or prothionamide/ethionamide, the shorter regimen is associated with more failure or relapse. Our findings, and concerns about the reliability and reproducibility of phenotypic DST for some of these drugs, reinforce the need to increase access to reliable DST.

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