EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Standardised shorter regimens *versus* individualised longer regimens for multidrug-resistant TB

Syed Abidi, Jay Achar, Mourtala Mohamed Assao Neino, Didi Bang, Andrea Benedetti, Sarah Brode, Jonathon R. Campbell, Esther Casas, Francesca Conradie, Gunta Dravniece, Philipp du Cros, Denis Falzon, Ernesto Jaramillo, Christopher Kuaban, Zhiyi Lan, Christoph Lange, Pei Zhi Li, Mavluda Makhmudova, Aung Kya Jai Maug, Dick Menzies, Giovanni Battista Migliori, Ann Miller, Bakyt Myrzaliev, Norbert Ndjeka, Jűrgen Noeske, Nargiza Parpieva, Alberto Piubello, Valérie Schwoebel, Welile Sikhondze, Rupak Singla, Mahamadou Bassirou Souleymane, Arnaud Trébucq, Armand Van Deun, Kerri Viney, Karin Weyer, Betty Jingxuan Zhang, Faiz Ahmad Khan

Please cite this article as: Abidi S, Achar J, Neino MMA, *et al*. Standardised shorter regimens *versus* individualised longer regimens for multidrug-resistant TB. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.01467-2019).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

TITLE PAGE

Standardised shorter regimens vs. individualised longer regimens for multidrug-resistant TB

Author Name	Contact	Highest degree	Affiliations
Syed Abidi	syed.abidi3@mail.mcgill.ca	BSc	McGill International TB Centre, Respiratory Epidemiology & Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill University & Research Institute of the McGill University Health Centre
Jay Achar	jay.achar@london.msf.org	MBBS	Médecins Sans Frontières/Doctors without Borders
Mourtala Mohamed Assao Neino	mourt2000@yahoo.fr	MD	National Tuberculosis Program, Niamey, Niger
Didi Bang	dvb@ssi.dk	MD	Statens Serum Institut
Andrea Benedetti	andrea.benedetti@mcgill.ca	PhD	Department of Epidemiology Biostatistics & Occupational Health, Faculty of Medicine, McGill University McGill International TB Centre, Respiratory Epidemiology & Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill University & Research Institute of the McGill University Health Centre
Sarah Brode	sarah.brode@westpark.org	MD	West Park Healthcare Centre, University Health Network, and University of Toronto
Jonathon R. Campbell	jonathon.campbell@mail.mcgill.ca	PhD	McGill International TB Centre, Respiratory Epidemiology & Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill University & Research Institute of the McGill University Health Centre
Esther Casas	esther.casas@joburg.msf.org	MD	Médecins Sans Frontières/Doctors without Borders
Francesca Conradie	fconradie@witshealth.co.za	MBChB	Department of Medicine, University of Witswatersrand, Johannesburg, South Africa
Gunta	gunta.dravniece@kncvtbc.org	MD	KNCV TB Foundation, The

Dravniece			Netherlands
Philipp du Cros	philipp.ducros@burnet.edu.au	MBBS	Burnet Institute; Médecins Sans Frontières UK
Denis Falzon	falzond@who.int	MD	World Health Organisation
Ernesto Jaramillo	jaramilloe@who.int	MD	World Health Organisation
Christopher Kuaban	ckuaban@yahoo.fr	MD	The University of Bamenda, Cameroon
Zhiyi Lan	zhiyi.lan@mail.mcgill.ca	MSc	McGill International TB Centre, Respiratory Epidemiology & Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill University & Research Institute of the McGill University Health Centre
Christoph Lange	clange@fz-borstel.de	MD	1. Research Center Borstel, Leibniz Lung Center, Borstel, Germany; 2. German Center for Infectio Research Clinical TB Unit, Borstel, Germany; 3. Respiratory Medicine & International Health, University of Lübeck, Lübeck, Germany; 4. Department of Medicine, Karolinska Institute, Stockholm, Sweden
Pei Zhi Li	Pei.li@mail.mcgill.ca	MSc	Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill University & Research Institute of the McGill University Health Centre
Mavluda Makhmudova	mavluda.makhmudova@kncvtbc.org	MD	KNCV Tajikistan
Aung Kya Jai Maug	aung@damienfoundation-bd.com	MD	Damien Foundation, Dhaka, Bangladesh
Dick Menzies	dick.menzies@mcgill.ca	MD	McGill International TB Centre, Respiratory Epidemiology & Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill University & Research Institute of the McGill University Health Centre
Giovanni Battista Migliori	gbmigliori@gmail.com	MD	WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, Italy
Ann Miller	ann_miller@hms.harvard.edu	PhD	Harvard Medical School, Department

			of Global Health and Social Medicine
Bakyt Myrzaliev	bakyt.myrzaliev@kncvtbc.org	MD	KNCV TB Foundation, Branch office KNCV in Kyrgyzstan
Norbert Ndjeka	Norbert.Ndjeka@health.gov.za	MD	National TB Programme, Republic of South Africa, Pretoria, South Africa
Jűrgen Noeske	jurgen.noeske@gmail.com	PhD	Independent Consultant
Nargiza Parpieva	nargizaparpieva@gmail.com	MD	**National TB Institute, Tashkent, Uzbekistan**
Alberto Piubello	apiubello@theunion.org	MD	International Union Against Tuberculosis and Lung Disease, Paris, France - Damien Foundation, Niamey, Niger
Valérie Schwoebel	vschwoebel@theunion.org	MD	International Union Against Tuberculosis and Lung Disease, Paris, France
Welile Sikhondze	Welile.sikhondze@gmail.com	MD	Eswatini Ministry of Health, National TB Control Program
Rupak Singla	drrupaksingla@yahoo.com	MD	National Institute of Tuberculosis and Respiratory Diseases, Delhi, India
Mahamadou Bassirou Souleymane	bachirsoul@gmail.com	MD	Damien Foundation, Niamey, Niger
Arnaud Trébucq	atrebucq@theunion.org	MD	International Union Against Tuberculosis and Lung Disease, Paris, France
Armand Van Deun	avandeun@theunion.org	MD	Institute of Tropical Medicine, Mycobacteriology Unit, Antwerp, Belgium
Kerri Viney	kerri.viney@hotmail.com	PhD	University of Sydney, Australia
Karin Weyer	weyerk@who.int	PhD	World Health Organisation
Betty Jingxuan Zhang	jingxuanbetty@hotmail.com	MSc	McGill International TB Centre, Respiratory Epidemiology & Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill University & Research Institute of the McGill University Health Centre
Faiz Ahmad Khan	faiz.ahmadkhan@mcgill.ca	MDCM	McGill International TB Centre, Respiratory Epidemiology & Clinical Research Unit, Centre for Outcomes Research & Evaluation, McGill

			University & Research Institute of the McGill University Health Centre

Corresponding Author:

Faiz Ahmad Khan

3D.60 - 5252 Boulevard de Maisonneuve O, Montréal, QC H4A 3S5

faiz.ahmadkhan@mcgill.ca

514 934 1934 ext 32129

Standardised shorter regimens vs. individualised longer regimens for multidrug-resistant TB

We sought to compare the effectiveness of two WHO-recommended regimens for the treatment of rifampin- or multidrug-resistant (RR/MDR) tuberculosis: 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 tuberculosis. We used propensity score matched, mixed-effects meta-regression to calculate adjusted odds ratios and adjusted risk differences (aRD) for failure or relapse, death within 12 months of treatment initiation, and loss to follow-up.

We included 2625/3378 (77.7%) individuals from 9 studies of shorter regimens, and 2717/13104 (20.7%) from 53 studies of longer regimens. Treatment success was higher with the shorter regimen than with longer regimens (pooled proportions: 80.0% vs. 75.3%), due to less loss to follow-up with the former (aRD, -0.15 95%CI:-0.17 to -0.12). The risk difference for failure or relapse was slightly higher with the shorter regimen overall (0.02, 95%CI:0 to 0.05), and greater in magnitude with baseline resistance to pyrazinamide (0.12, 95%CI:0.07 to 0.16), prothionamide/ethionamide (0.07, 95%CI:-0.01 to 0.16), or ethambutol (0.09, 95%CI:0.04 to 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 as compared to individualised longer regimens, and with more failure/relapse in the presence of resistance to component medications. Our findings support the need to improve access to reliable drug susceptibility testing.

Manuscript

Introduction

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

Since 2016, WHO guidelines have included the option of treating RR/MDR tuberculosis with a standardised regimen of 9 to 12 months in duration ('the shorter regimen') instead of an individualised regimen of at least 20 months.[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 as compared to individualised longer regimens remains unclear. In a recently published randomised clinical trial comparing the shorter regimen to longer regimens composed per 2016 WHO guidelines, the shorter regimen was non-inferior with respect to overall treatment success, but rates of non-conversion/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 to 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 treatment of RR/MDR tuberculosis.[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, standardization of outcomes, use of multivariable analyses to adjust for potential confounding by other co-variates, 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 tuberculosis.

Regimen definitions

We defined shorter regimens as standardised regimens with an intended duration of 9 to 12 months including 4 to 6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, ethambutol, and high-dose isoniazid, followed by 5 to 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.

We defined longer regimens per 2016 WHO guidelines as individualised regimens that included a later-generation fluoroquinolone and a second-line injectable amongst at least five anti-tuberculosis medications considered to be effective based on drug susceptibility testing (DST), or, at least four 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 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 tuberculosis 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 tuberculosis, with clear descriptions of treatment regimens[13,15,19] In this update, investigators of previously identified studies provided data on additional patients from their centers 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-tuberculosis drugs), methods and dates of tuberculosis 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, 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 to 12 months (**Appendix 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 tuberculosis 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 tuberculosis 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 tuberculosis (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 regimens 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 treated for less than the minimal recommended duration (we used 8 months and 17.5 months as cut-offs for minimal duration). From the shorter regimens group, we excluded patients whose treatment was prolonged for more than 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-tuberculosis drugs, and extensiveness of tuberculosis disease. We classified disease as extensive if sputum was smear-positive or, when smear results were missing, if chest radiographs demonstrated cavities. If cavitation was not reported, we classified disease as extensive if there were bilateral abnormalities on chest radiographs.

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), and 95% confidence intervals (95%CI), for the following outcomes: (i) failure or relapse versus success; (ii) death versus success; and (iii) loss to follow-up versus success, failure or relapse. Estimates were calculated overall (including all patients), and within pre-specified sub-groups 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-tuberculosis. In the second, we compared the two regimens for the treatment of fluoroquinolone-resistant RR/MDR tuberculosis.

We interpreted associations based on adjusted ORs rather than RDs, 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 CI 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%CI was greater than 0.95, and a negative association (i.e. with OR point estimate < 1) as important if the upper bound of the 95%CI was less than 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 caliper 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: "metaforV2.0-0", "lme4V1.1-21", and "mice V3.4.0".[29-31] The protocol can be obtained by contacting the corresponding author.

Role of the funding source

The WHO Global TB Programme funded the study and conducted the public call and collection of unpublished data. Employees of the Global TB Programme participated in data collection and analysis. The WHO Drug-Resistant TB Guidelines Development Group provided input on the statistical analysis plan, and reviewed and discussed our results when updating their guidelines in 2018. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study & patient selection

We identified 6 studies of shorter regimens and 43 of longer regimens from previously published systematic reviews,[13,15,19] to which we added 13 studies (3 shorter, 10 longer) identified through the WHO public call (**Appendix Figure A1**). Individual-level data were available for 3378 patients treated with shorter regimens and 13104 treated with longer regimens. No important issues were identified in checking the individual patient data.

Table 1 enumerates the reasons why we excluded 753/3378 (22%) individuals treated with shorter regimens, and 10387/13104 (79%) treated with longer regimens. Of those excluded from the longer regimens, 5012/10387 (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 regimens group, whereas exclusions due to treatment durations not meeting recommendations were more common in the shorter regimens group. The proportion of individuals excluded due to missing data on duration or outcomes was higher in the longer regimens group. In both groups, the proportion excluded due to deaths occurring after month 12 of treatment was small (<1%). Overall, we included 2625/3378 (77.7%) individuals from 9 studies[7,32-40] of shorter regimens,

and 2717/13104 (20.7%) from 39 studies of longer regimens.[41-85] Of the 48 included studies, 39/48 (81%) were of high quality, 8/38 (17%) moderate, and 1/38 (2%) low (**Appendix Table A2**).

Description of included patients and regimens

Table 2 summarizes patient characteristics and DST results. Distributions of age and gender were similar between the two groups. Longer regimen treated patients were more likely to be people living with HIV (PLWH), and to have cavitary tuberculosis. Those treated with the shorter regimen were more likely to have smear-positive tuberculosis, bilateral disease, previous treatment with first-line drugs, and to have been treated in low-middle or low-income countries (98.4% vs. 16.6%). Numbers of PLWH not on antiretroviral therapy were small in both groups. Prevalence of resistance to pyrazinamide, prothionamide/ethionamide, and ethambutol, were similar between the two groups. Resistance to pyrazinamide, ethambutol, and prothionamide/ethionamide were correlated (**Appendix Table A3**). Few patients had DST for clofazimine, PAS, cycloserine, and linezolid.

Regimen composition is summarised in **Table 3**. Moxifloxacin was the most common fluoroquinolone in both regimens. Only 2/2717 (0.1%) patients treated with longer regimens received gatifloxacin, versus 1040/2625 (39.6%) of those 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 treated with the shorter regimen. In the longer regimens group, bedaquiline was used in 320/2717 (11.8%) patients, linezolid in 244/2717 (9.0%), a carbapenem in 21/2717 (0.7%), and delamanid in 16/2717 (0.6%).

Aggregate data meta-analyses

The pooled rate of treatment success was higher with the shorter regimen (80%) as compared to longer regimens (75.3%) (**Table 4**). Fewer shorter regimen treated patients were lost to follow-up (4.2% vs. longer: 14.6%), and more experienced failure or relapse (shorter: 3.6% vs. longer: 2.7%), and death (shorter: 7.6% vs. longer: 4.6%). Heterogeneity was high for each outcome, for both regimens. Forest plots are in **Appendix Figures A2-A4**.

Individual patient data meta-analyses

In univariable analyses (**Appendix Table A4**), failure or relapse were 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 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, 95CI:0.07 to 0.16), prothionamide/ethionamide (aRD, 0.07, 95CI:-0.01 to 0.16), and ethambutol (aRD 0.09, 95CI:0.04 to 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 (see **Appendix Table A5**, aRD 0.10, 95CI:0.05 to 0.15). Death during the first 12 months of 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, 95CI:-0.17 to -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 **Appendix 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%, longer 57.4%), and previous first-line treatment was more common (shorter 82.5%, 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, and prothionamide/ethionamide, were each more common in the longer regimens group (pyrazinamide: shorter 59%, longer 77.3%; ethambutol: shorter 67.6%, longer 78.3%; prothionamide/ethionamide: 50.2% vs 61.9%). As shown in **Table 8**, moxifloxacin- or levofloxacin-based shorter regimens were associated with greater risk of death compared to 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 to 0.22). There were no important differences in failure/relapse and loss to follow-up.

Sensitivity analyses

When patients with isoniazid-susceptible RR-tuberculosis were included (**Appendix Table A7A**), failure/relapse was not associated with type of regimen, but death was weakly associated with the shorter regimen (aOR 1.2, 95%CI:0.96 to 1.5; aRD 0.02, 95%CI:-0.01, 0.05). For RR/MDR tuberculosis additionally resistant to fluoroquinolones, treatment with the shorter regimen was associated with increased failure/relapse (aOR 15.0 95%CI: 2.8-80.6; aRD 0.33, 95%CI: 0.22 to 0.44) (**Appendix Table A7B**).

Discussion

In this individual patient-level data meta-analysis on the treatment of RR/MDR tuberculosis 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 as compared to individualised longer regimens composed per 2016 WHO guidelines. In adjusted analyses, we observed the standardised shorter regimen was associated with a higher risk of bacteriologic 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 amongst 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) to 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 non-inferiority of the shorter regimen vs. longer standardized ones, for a composite endpoint of bacteriologic outcomes, death, and treatment completion.[3,4] In STREAM, the proportion not completing treatment per protocol was higher with the longer regimen (30.3% vs. 6.7%), there was a non-significant increase of unfavourable microbiologic outcomes with the shorter regimen (relative risk of sputum culture non-conversion 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 tuberculosis.[86,87] In a number of our analyses, resistance was associated with greater failure/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[88-90]—including amongst the authors of this study. This is because the association of failure/relapse with resistance to pyrazinamide, ethambutol, or prothionamide/ethionamide in the treatment of RR/MDR TB was not significant in some studies,[7,32] and because concerns exist about the accuracy of DST to ethambutol and prothionamide/ethionamide.[90-92]

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 from countries of high or upper-middle income (83.4%). Programmes in the latter settings are likely to have had greater resources, including for the management of co-morbidities 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 or higher 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 bedaquiline, clofazimine, and fluoroquinolones were found to have a low risk of adverse events, whereas risks were high with second-line injectables and linezolid.[93] Fourth, because we did not apply an upper limit to duration used to define longer regimens, it is possible that confounding by indication for prolonged treatment could have resulted in underestimation of success rates associated with the longer regimen. Fifth, because some patients lost-to-follow-up during treatment may have been undiagnosed failure cases, it is possible that failure or relapse were less likely to be detected in the longer regimen. Finally, caution is warranted in interpretation of differences in loss to follow-up as non-completion of treatment with a shorter regimen may carry a greater risk of death or failure than non-completion 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% treated with the longer regimen 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 generalizability and strengthened the evidence base for shorter regimens. 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 on-going 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.

Conclusion

Compared to individualised longer regimens for the treatment of RR/MDR tuberculosis that is 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 and 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.

Authors Contributions

FAK, DM, AB, PDC, JRC, DF, ZL, AP, VS, and AT, designed the study and protocol. JA, MMAN, MAKJ, DB, SKB, EC, FC, GD, PDC, CK, AM, BM, GBM, MM, JN, NN, AP, NP, MBS, RS, VS, WS, and AT, contributed data to the meta-analysis. SA, FAK, AB, JRC, PL, ZL, DM, and JZ did the data analysis. FAK wrote the initial draft of the manuscript, and all authors provided critical input and revisions to the draft manuscripts, and approved the final manuscript.

Declaration of Interests

FAK reports operating grants from the World Health Organisation for the conduct of the study. SKB reports grants from Insmed, personal fees from Boehringer Ingelheim, personal fees from Astra-Zeneca , grants from Canadian Institutes for Health Research, outside the submitted work. PDC reports he was previously a member of the Steering Committee and protocol writing committee for The PRACTECAL randomised controlled trial of three novel 6-month MDR-TB regimens; he has undertaken a paid consultancy between TB Alliance and Burnet Institute to investigate applicability of the TB-Nix regimen (a novel short MDR-TB regimen) to Papua New Guinea. CL reports personal fees from Chiesi, personal fees from Gilead, personal fees from Janssen, personal fees from Lucane, personal fees from Novartis, personal fees from Oxoid, personal fees from Berlin Chemie, personal fees from Thermofisher, outside the submitted work. AM reports The Eli Lilly Foundation MDR-TB Partnership supported part of her salary in 2015-2016 through a grant to Salmaan Keshavjee, Harvard Medical School, outside the submitted work; the grant also paid for AM’s travel to a meeting in July of 2016.

Table 1: Selection of patients from individual patient databases

Individuals with >1 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.

	Shorter	**Longer**
In initial database	**3378**	**13104**
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 IPD-MA	**447**	**5375**
Isoniazid susceptible TB	210	15
Not treated with a shorter regimen[*]	151	Not applicable
Not treated with later generation fluoroquinolone	Not applicable	2954
Not treated with second-line injectable	Not applicable	917
Other	23	0
Duration or Outcome data missing	52	1852
Not Treated with $\geq$ 4 effective drugs & PZA, or $\geq$ 5 effective drugs[†]	Not applicable	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**

[*] 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. PAS, Cycloserine/Terizidone, Bedaquline)

[#] 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.

[†] Amongst those otherwise meeting criteria for inclusion.

[††] Amongst those otherwise meeting criteria for inclusion. See Methods for rationale.

Table 2: Clinical characteristics of included patients

	Shorter, N=2625	Longer, N=2717
Mean Age (standard deviation)	35.4 (±13.0)	36.6 (±12.4)
Children & adolescents (age < 16 years)	53 (2.0%)	29 (1.1%)
Male Sex	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 CXR	501 (40.1%)	465 (52.2%)
Bilateral disease on CXR	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%)*
PAS		
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%)*

† Patients were classified as having extensive disease if they were smear positive, and 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.

Table 3: Regimen composition of shorter and longer regimens included in analyses

	Shorter	Longer
Number 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%)
PAS	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, in months* (Median, IQR)	4 (3.9, 4)	7.8 (6.1, 9.1)
Duration of treatment, in months* (Median, IQR)	9 (8.9, 9.7)	21.6 (19.5, 24)

* Amongst successfully treated patients.

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% (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=0.6*	*I^2=85 %, τ^2=0.51.0*
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=0.8*	*I^2=69%, τ^2=0.74*	*I^2=76 %, τ2=0.5*

Table 5: Comparison of shorter regimens and individualised longer regimens for outcome of failure or relapse vs 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		
				N Pairs	aOR (95%CI)	aRD (95% CI)
Fail/relapse vs Success						
Overall	9, 38	118/2282	112/1926	1926	**2.0 (0.96, 4.0)**	**0.02 (0.00, 0.05)**
HIV status strata						
PLWH	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)**[F]	**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)**[F]	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)**[F]	**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)

Confidence intervals suggestive of increased odds or risk of failure or relapse with the shorter regimen are in bold red font.

Confidence intervals suggestive of lower odds or risk of failure or relapse with the shorter regimen are in bold black font.

All models adjust for age, sex, HIV status, previous treatment with first-line tuberculosis medications, and extensiveness of disease. Results were adjusted as described in the Methods. aOR: adjusted odds ratio; aRD: adjusted risk difference; PLWH: people living with HIV; DST: drug susceptibility testing

[F]: aOR calculated from fixed effect model.

†: analyses restricted to patients with DST-confirmed fluoroquinolone susceptibility (i.e. excluding those with no DST data for fluoroquinolones)

Table 6: Comparison of shorter regimens and individualised longer regimens for outcome of death during the first 12 months of treatment vs success, using individual patient-data meta-analysis

	Studies Shorter, Longer	Shorter Events/ Total	Longer Events/ Total	Propensity score matched multivariable meta-regression		
				N Pairs	aOR (95%CI)	aRD (95% CI)
Death vs Success						
Overall	9, 37	201/2365	265/2079	2079	1.2 (0.95, 1.6)	0.02 (-0.01, 0.05)
HIV status strata						
PLWH	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)

All models adjust for age, sex, HIV status, previous treatment with first-line tuberculosis medications, and extensiveness of disease. Results were adjusted as described in the Methods. aOR: adjusted odds ratio; aRD: adjusted risk difference; PLWH: people living with HIV; DST: drug susceptibility testing

[†]: analyses restricted to patients with DST-confirmed fluoroquinolone susceptibility (i.e. excluding those with no DST data for fluoroquinolones)

Table 7: Comparison of shorter regimens and individualised longer regimens for outcome of loss to follow-up vs success, using individual patient-data meta-analysis

	Studies Shorter, Longer	Shorter Events/ Total	Longer Events/ Total	Propensity score matched multivariable meta-regression		
				N Pairs	aOR (95%CI)	aRD (95% CI)
Lost vs Success, Fail/relapse						
Overall	9, 37	142/2424	526/2452	2424	**0.2 (0.2, 0.3)**	**-0.15 (-0.17, -0.12)**
HIV status strata						
PLWH	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)**

Confidence intervals suggestive of lower odds or risk of loss to follow-up with the shorter regimen are in bold black font.

All models adjust for age, sex, HIV status, previous treatment with first-line tuberculosis medications, and extensiveness of disease. Results were adjusted as described in the Methods. aOR: adjusted odds ratio; aRD: adjusted risk difference; PLWH: people living with HIV; DST: drug susceptibility testing

[†]: analyses restricted to patients with DST-confirmed fluoroquinolone susceptibility (i.e. excluding those with no DST data for fluoroquinolones)

Table 8: Comparison of moxifloxacin- or levofloxacin-based shorter regimens to longer regimens meeting WHO 2018 composition and duration criteria, using individual patient-data meta-analysis, amongst patients with rifampin or multidrug-resistant tuberculosis confirmed susceptible to fluoroquinolones

	Studies Shorter, Longer	Shorter Events/ Total	Longer Events/ Total	Propensity score matched multivariable meta-regression		
				N Pairs	aOR (95%CI)	aRD (95% CI)
Fail/relapse vs 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 vs Success	9, 9	79/879	13/138	138	**2.5 (1.0, 6.3)**	0.11 (-0.01, 0.22)
Lost vs Success, Fail/relapse	9, 10	44/925	14/149	149	0.6 (0.1, 4.5)	-0.01 (-0.09, 0.07)

Confidence intervals suggestive of increased odds or risk of death with the shorter regimen are in bold red font.

All models adjust for age, sex, HIV status, previous treatment with first-line tuberculosis medications, and extensiveness of disease. Results were adjusted as described in the Methods. aOR: adjusted odds ratio; aRD: adjusted risk difference.

References

1. World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organization; 2018.
2. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis - 2016 update. Geneva: World Health Organization; 2016.
3. Nunn AJ, Phillips PPJ, Meredith SK, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. *N Engl J Med* 2019.
4. World Health Organization. Position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results. Geneva, Switzerland: WHO, 2018.
5. Javaid A, Ahmad N, Khan AH, Shaheen Z. Applicability of the World Health Organization recommended new shorter regimen in a multidrug-resistant tuberculosis high burden country. 2016: 1601967.
6. Rusen ID, Chiang CY. Building the evidence base for shortened MDR-TB treatment regimens. *Int J Tuberc Lung Dis* 2018; **22**(1): 1-2.
7. Trebucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis* 2018; **22**(1): 17-25.
8. Van Deun A, Chiang C-Y. Shortened multidrug-resistant tuberculosis regimens overcome low-level fluoroquinolone resistance. 2017; **49**(6): 1700223.
9. Varaine F, Guglielmetti L, Mitnick CD. Reply: Benefit of the Shorter Multidrug-Resistant Tuberculosis Treatment Regimen in California and Modified Eligibility Criteria. *Am J Respir Crit Care Med* 2017; **196**(11): 1490-1.
10. Walsh KF, Souroutzidis A, Vilbrun SC, et al. Potentially High Number of Ineffective Drugs with the Standard Shorter Course Regimen for Multidrug-Resistant Tuberculosis Treatment in Haiti. 2018: tpmd180493.
11. Sotgiu G, Tiberi S, D'Ambrosio L, et al. Faster for less: the new "shorter" regimen for multidrug-resistant tuberculosis. *Eur Respir J* 2016: ERJ-01249-2016.
12. World Health Organization. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) Geneva, Switzerland: WHO, 2018.
13. Ahmad Khan F, Salim MAH, du Cros P, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J* 2017; **50**(1).
14. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012; **9**(8): e1001300.
15. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDRTB treatment, Ahmad N, Ahuja SD, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; **392**(10150): 821-34.
16. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011; **46**(3): 399-424.
17. Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval Health Prof* 2002; **25**(1): 76-97.
18. World Health Organization. The Use of Delamanid in the Treatment of Multidrug-Resistant Tuberculosis in Children and Adolescents: Interim Policy Guidance. Geneva, Switzerland: WHO; 2016.
19. Bastos M, et al. An Updated Systematic Review and Meta-Analysis for Treatment of Multidrug-Resistant Tuberculosis. *European Respiratory Journal, requested revision under consideration* 2016.
20. World Health Organization. Public call for individual patient data on treatment of rifampicin and multidrug-resistant (MDR/RR-TB) tuberculosis. 2018. http://www.who.int/tb/features_archive/public_call_treatment_RR_MDR_TB/en/.
21. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. 2016; **355**: i4919.
22. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision. WHO/HTM/TB/2013.2. Geneva; 2013.
23. World Health Organization. Stop TB Dept. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2008.
24. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. *J Clin Epidemiol* 2008; **61**(1): 41-51.
25. Wasserstein RL, Lazar NA. The ASA's statement on p-values: context, process, and purpose. *The American Statistician* 2016; **70**(2): 129-33.
26. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *International journal of methods in psychiatric research* 2011; **20**(1): 40-9.
27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011; **30**(4): 377-99.

28. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *2011* 2011; **45**(3): 67 %J Journal of Statistical Software.
29. Bates D, Mächler M, Bolker B, Walker SJapa. Fitting linear mixed-effects models using lme4. 2014.
30. van Buuren S, Groothuis-Oudshoorn KJ. mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software* 2010: 1-68.
31. Viechtbauer WJ. Conducting meta-analyses in R with the metafor package. *Stat Softw* 2010; **36**(3): 1-48.
32. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis* 2014; **18**(10): 1180-7.
33. Kyrgyz Republic and KNCV. Unpublished data. 2018.
34. Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Abena Foe JL, Trebucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis* 2015; **19**(5): 517-24.
35. Médecins Sans Frontières Manson Unit, Ministry of Health Uzbekistan. Unpublished data. 2018.
36. Médecins Sans Frontières Operational Center Amsterdam, MSF-OCA Swaziland, Ministry of Health Swaziland. Unpublished data. 2018.
37. Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis* 2014; **18**(10): 1188-94.
38. Republic of Tajikistan TB Centre and KNCV. Unpublished data. 2018.
39. South African Ministry of Health. Unpublished Data. 2018.
40. Van Deun A, Maug AK, Hamid Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Resp Crit Care Med* 2010; **182**(5): 684-92.
41. Anderson LF, Tamne S, Watson JP, et al. Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007. *Euro Surveill* 2013; **18**(40).
42. Anger HA, Dworkin F, Sharma S, Munsiff SS, Nilsen DM, Ahuja SD. Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, New York City, 2000-06. *J Antimicrob Chemother* 2010; **65**(4): 775-83.
43. Bang DL, T.; Thomsen, V. O.; Andersen, A. B. Multidrug-resistant tuberculosis: Treatment outcome in Denmark, 1992-2007. *Scand J Infect Dis* 2010; **42**(4): 288-93.
44. Barry PM, Flood J, Lowenthal P, Westenhouse J, California Department of Public Health. Unpublished data (California, USA). 2016.
45. Bonnet M, Pardini M, Meacci F, et al. Treatment of tuberculosis in a region with high drug resistance: outcomes, drug resistance amplification and re-infection. *PLoS ONE* 2011; **6**(8): e23081.
46. Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017; **49**(5).
47. Brode S, West Park Healthcare Centre. Unpublished data (Toronto, Canada). 2016.
48. Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial Versus Acquired Second-Line Drug Resistance. *Clin Infect Dis* 2016; **62**(4): 418-30.
49. Chan ED, National Jewish Health. Unpublished data (Denver, USA). 2016.
50. Chang KC, Leung CC, Yew WW, et al. Pyrazinamide may improve fluoroquinolone-based treatment of multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2012; **56**(11): 5465-75.
51. Chang KC, Yew WW, Cheung SW, et al. Can intermittent dosing optimize prolonged linezolid treatment of difficult multidrug-resistant tuberculosis? *Antimicrob Agents Chemother* 2013; **57**(7): 3445-9.
52. Charles M, Vilbrun SC, Koenig SP, et al. Treatment outcomes for patients with multidrug-resistant tuberculosis in post-earthquake Port-au-Prince, Haiti. *Am J Trop Med Hyg* 2014; **91**(4): 715-21.
53. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; **371**(8): 723-32.
54. Eker B, Ortmann J, Migliori GB, et al. Multidrug- and extensively drug-resistant tuberculosis, Germany. *Emerg Infect Dis* 2008; **14**(11): 1700-6.
55. Guglielmetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Respir J* 2017; **49**(3).
56. Guglielmetti L, Le Du D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; **60**(2): 188-94.
57. Hughes J, Isaakidis P, Andries A, et al. Linezolid for multidrug-resistant tuberculosis in HIV-infected and -uninfected patients. *Eur Respir J* 2015; **46**(1): 271-4.
58. Isaakidis P, Varghese B, Mansoor H, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. *PLoS ONE* 2012; **7**(7): e40781.
59. Jarlsberg L, Nahid P. Unpublished data (San Francisco, USA). 2016.

60. Jeong BH, Jeon K, Park HY, et al. Outcomes of pulmonary MDR-TB: impacts of fluoroquinolone resistance and linezolid treatment. *J Antimicrob Chemother* 2015; **70**(11): 3127-33.
61. Jo KW, Lee SD, Kim WS, Kim DS, Shim TS. Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2014; **18**(1): 39-43.
62. Kempker RR, Kipiani M, Mirtskhulava V, Tukvadze N, Magee MJ, Blumberg HM. Acquired Drug Resistance in Mycobacterium tuberculosis and Poor Outcomes among Patients with Multidrug-Resistant Tuberculosis. *Emerg Infect Dis* 2015; **21**(6): 992-1001.
63. Koh WJ, Kang YR, Jeon K, et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; **67**(6): 1503-7.
64. Kwak N, Kim HR, Yoo CG, Kim YW, Han SK, Yim JJ. Changes in treatment outcomes of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2015; **19**(5): 525-30.
65. Laniado-Laborin R, Estrada-Guzman J, Perez H, Batiz-Armenta F, Alcantar-Schramm JM. Treatment of multidrug-resistant tuberculosis in a high-prevalence region through a binational consortium. *Int J Tuberc Lung Dis* 2012; **16**(5): 610-1.
66. Marks SM, Flood J, Seaworth B, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005-2007. *Emerg Infect Dis* 2014; **20**(5): 812-21.
67. Milanov V, Falzon D, Zamfirova M, et al. Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria, 2009-2010. *International journal of mycobacteriology* 2015; **4**(2): 131-7.
68. Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *Int J Tuberc Lung Dis* 2015; **19**(8): 979-85.
69. Podewils LJ, Gler MT, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS ONE* 2013; **8**(7): e70064.
70. Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J* 2016; **47**(2): 564-74.
71. Riekstina V, Leimane V, Cirule A, Kuksa L, Latvia National TB registry. Unpublished data (Latvia). 2016.
72. Smith SE, Ershova J, Vlasova N, et al. Risk factors for acquisition of drug resistance during multidrug-resistant tuberculosis treatment, Arkhangelsk Oblast, Russia, 2005-2010. *Emerg Infect Dis* 2015; **21**(6): 1002-11.
73. Tiberi S, Payen MC, Sotgiu G, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; **47**(4): 1235-43.
74. Tiberi S, Sotgiu G, D'Ambrosio L, et al. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; **47**(6): 1758-66.
75. van Altena R, de Vries G, Haar CH, et al. Highly successful treatment outcome of multidrug-resistant tuberculosis in the Netherlands, 2000-2009. *Int J Tuberc Lung Dis* 2015; **19**(4): 406-12.
76. Viiklepp P, Estonian TB Registry. Unpublished data (Estonia). 2016.
77. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; **360**(23): 2397-405.
78. endTB investigators. Unpublished data. 2018.
79. Guglielmetti L. Unpublished data (France). 2018.
80. Ndjeka N. Unpublished data (South Africa). 2018.
81. Fox G. Unpublished data (Australia). 2018.
82. Kuksa L. Unpublished data (Latvia). 2018.
83. Barkane. Unpublished data (Latvia, Delamanid). 2018.
84. Skrahina A. Unpublished data (Belarus). 2018.
85. Vasilyeva I. Unpublished data (Russia). 2018.
86. Sun F, Li Y, Chen Y, et al. Introducing molecular testing of pyrazinamide susceptibility improves multidrug-resistant tuberculosis treatment outcomes: a prospective cohort study. *Eur Respir J* 2019; **53**(3).
87. Bastos ML, Hussain H, Weyer K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. *Clin Infect Dis* 2014; **59**(10): 1364-74.
88. Yakrus MA, Driscoll J, McAlister A, et al. Molecular and Growth-Based Drug Susceptibility Testing of Mycobacterium tuberculosis Complex for Ethambutol Resistance in the United States. *Tuberc Res Treat* 2016; **2016**: 3404860.
89. Migliori GB, Sotgiu G, Rosales-Klintz S, et al. ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update. *Eur Respir J* 2018; **51**(5): 1702678.

90. World Health Organization. Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. WHO/CDS/TB/2018.24; 2018.
91. Horne DJ, Pinto LM, Arentz M, et al. Diagnostic accuracy and reproducibility of WHO-endorsed phenotypic drug susceptibility testing methods for first-line and second-line antituberculosis drugs. *J Clin Microbiol* 2013; **51**(2): 393-401.
92. Lakshmi R, Ramachandran R, Kumar DR, et al. Revisiting the susceptibility testing of Mycobacterium tuberculosis to ethionamide in solid culture medium. *Indian J Med Res* 2015; **142**(5): 538-42.
93. Lan Z, Ahmad N, Baghaei P, et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 2019; **in press.**

Appendix Table A1: Outcome definitions from cohort studies of shorter regimens

No	Study, Ref	Cure	Treatment Completed	Treatment Failure	Lost to follow-up (default)	Relapse
1	Van Deun Aung	Completed treatment without evidence of failure clinically and bacteriologically (negative ≥3 occasions over 5 months, and 1 of those taken at the end of treatment)[1]	Full course of treatment completed but incomplete documentation by sputum smears according to the criteria of cure.	•Treatment stopped at ≥6 months due to lack of response, or •Patients reverting to active TB without interruption of treatment with bacteriological evidence, or •Treatment definitively stopped for ≥2 drugs because of side-effects	Interruption of treatment for at least 2 months.	Recurrence clinically and bacteriological positive, and/ confirmed by positive culture on at at least two sputum specimens after cure or treatment completion, unless shown by fingerprinting to represent a different strain from baseline
2	Uzbekistan	•Completed treatment according to programme protocol •≥4 negative cultures from samples collected at least 30 days apart within the final 5 months of treatment •1 positive culture permitted if followed by ≥3 consecutive negative cultures taken at least 30 days apart in the final 3 months of treatment	An MDR TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final months of treatment) or otherwise, completion of treatment with documented bacteriological conversion persisting through the end of treatment, but fewer than five negative cultures.	•No negative culture by the end of month 5 of a prolonged intensive phase, •2 cultures positive during the continuation phase or 1 culture positive during the last 3 months of treatment, • Early treatment termination because of poor response or adverse events	An MDR TB patient who dies for any reason during the course of MDR TB treatment and is not already classified as a treatment failure prior to death.	An MDR TB patient who meets the criteria of cured or completed short course of treatment and at any time during the follow up period (first year after treatment completion) is subsequently diagnosed with at least one sample of bacteriologically positive TB by culture
3	Swaziland	•Completed treatment according to programme protocol •≥5 consecutive negative cultures from samples collected at least 30 days apart •1 positive culture permitted if followed by ≥3 consecutive negative cultures taken at least 30 days apart	An MDR TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final months of treatment) or otherwise, completion of treatment with documented bacteriological conversion persisting through the end of treatment, but fewer than five negative cultures. Treatment completion will only be an outcome for patients that are not able to produce sputum; in case of patients where the lack of bacteriological results is due to other reasons the outcome will be registered as "other" in order to avoid misclassification.	•No negative culture by the end of month 6 of a prolonged intensive phase, •Culture positive during the continuation phase: 2 cultures positive (continuation phase) or 1 culture positive (last 3 months), • Early treatment termination because of poor response or adverse events	An MDR TB patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval and not meeting the criteria for failure.	Relapse: An MDR TB patient who meets the criteria of cured or completed short course of treatment and at any time during the follow up period (first year after treatment completion) is subsequently diagnosed with at least one sample of bacteriologically positive MDR TB by culture and DST of the same strain found in initial diagnosis, proven by molecular techniques (Mycobacterium tuberculosis DNA fingerprinting). Re-infection: recurrent disease as defined for a relapse, with a strain showing a molecular pattern different from the initial isolate.
4	Kuaban	•Completed treatment according	An MDR-TB patient who has completed treatment	•Regimen change •Lack of	An MDR patient whose	Patient having been declared "cured" or

[1] Exclude: positive cultures representing different strain from baseline

		to the programme's protocol and has ≥5 consecutive negative cultures, each at least 30 days apart •1 positive culture permitted if followed by ≥3 consecutive negative cultures taken at least 30 days apart	according to country protocol but does not meet the definition for cure or treatment failure due to lack of bacteriological results (i.e. fewer than five cultures were performed in the final 8 months of therapy).	bacteriological response and lack of clinical improvement at 6 months of treatment, or •Bacteriological reversion with concomitant clinical deterioration after initial response occurring after at least 6 months of treatment, or •Adverse drug events	treatment was interrupted for two or more consecutive months for any reason without medical approval.	"treatment completed" presenting with a new episode of TB disease (whatever form of TB also instructions where given to declare "relapse" preferentially in bacteriologically confirmed cases)
5	Piubello	•Completed treatment and ≥5 consecutive negative cultures collected at least 30 days apart during the last 8 months of treatment, or •1 positive culture without concurrent clinical deterioration, followed by ≥4 consecutive negative cultures (2008-2013) •Treatment completed as recommended by the national policy without evidence of failure, and ≥3 consecutive cultures taken at least 30 days apart are negative after the intensive phase (2014-2016)	Treatment completed with documented bacteriological conversion but not meeting the definition for cure (2008-2013). Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase (2014-2016).	•≥ 2/5 cultures positive in the final 8 months of treatment, or • 1 of the final 3 cultures positive, or •Treatment stopped definitively due to adverse drug reactions, terminated or permanent regimen change	A patient whose treatment was interrupted for 2 consecutive months or more	Patient having been declared cured or treatment completed with a positive culture during the 24 months follow-up after cure except if molecular tests prove an infection with a different strain from the initial (2008-2014). Patient having been declared cured or treatment completed with a positive culture during the 12 months follow-up after cure except if molecular tests prove an infection with a different strain from the initial (2015-2016).
6	Trebucq	•Completed treatment without evidence of failure and ≥3 consecutive negative cultures taken at least 30 days apart	Same as latest WHO definition	• Positive culture after 6 months of treatment (except when preceded by 1 negative and followed by at least 2 negative cultures)	Same as latest WHO definition	Same as latest WHO definition
7	Tajikistan	•Completed treatment as recommended by the national policy without evidence of failure, and •≥3 consecutive negative cultures taken at least 30 days apart after the intensive phase	Treatment completed as recommended by the national policy without evidence of failure BUT no record that 3 or more consecutive cultures taken at least 30 days apart, are negative after the intensive phase.	•Treatment terminated or need for permanent regimen change of ≥2 anti-TB drugs because of: •Lack of conversion by the end of intensive phase, or •Bacteriological (i.e. culture) reversion in the continuation phase after the conversion to negative, or •Evidence of additional	A patient whose treatment was interrupted for two consecutive months or more.	A DR-TB patient who meets the criteria of cured or completed short course of treatment and at any time within the first year after treatment completion is subsequently diagnosed with at least one sample of bacteriologically positive DR-TB by culture and DST.

				acquired resistance to FQ or SL, or •Adverse drug reactions		
8	Kyrgyzstan	•Completed treatment as recommended by the national policy without evidence of failure, and •≥ 3 consecutive negative cultures taken at least 30 days apart after the intensive phase	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.	Treatment terminated or permanent regimen change of ≥2 anti-TB drugs because of: •Lack of conversion by the end of intensive phase, or •Bacteriological reversion in the continuation phase after conversion to negative, or •Evidence of additional acquired resistance to FQ or SL, or •Adverse drug reactions	A patient whose treatment was interrupted for 2 consecutive months or more (note: this is called lost to follow-up; "default" is not used)	Not defined
9	South Africa	•Completed treatment of ≥9 months •TB culture conversion • ≥3 consecutive negative TB cultures during continuation phase (at least 30 days apart) •No evidence of clinical deterioration	•A patient who has had TB culture conversion •Received treatment for a total duration of 9 months or more •Has less than 3 consecutive negative TB Cultures during continuation phase (30 days apart) •No evidence of clinical deterioration	• Patient failed to culture convert by month 4 • In final 6 months of treatment ≥ 2 of 5 cultures are positive, clinical condition deteriorating • Treatment stopped on clinical grounds • ≥ 2 new drugs added because of poor clinical response	A patient with Treatment interrupted for: a. >= 2 consecutive months b. Any reason without medical approval	Not an outcome in the programme

Appendix Table A2. Quality assessment of included studies of (a) standardised shorter regimens, and (b) longer regimens.
Table A2a.

Shorter Regimen Database	Sampling method[†]	Info on DST SLI	Info on DST FQN	Participation rate[¶]	Lost to follow-up rate	Outcome definitions[ø]	Info on Age	Info on HIV[††]	Info on TB Tx history	Quality
Bangladesh [1,2]	Census	93%	93%	100%	7%	Study specific	100%	Not applied	100%	High
Uzbekistan MSF [3]	Census	78%	82%	100%	10%	Study specific /WHO 2013	100%	Not applied	100%	Moderate
Swaziland MSF [4]	Census	53%	55%	100%	0%	Study specific /WHO 2013	100%	100%	23%	Moderate
Cameroon[5]	Census	79%	79%	100%	2%	Study specific	100%	99%	98%	Moderate
Niger[6]	Census	98%	97%	100%	2%	Study specific	100%	96%	100%	High
Union 9 country[7]	Census	58%	59%	98%	5%	Study specific/ WHO 2013	100%	100%	100%	Moderate
*Tajikistan [8]	Census	82%	82%	100%	6%	WHO 2013	100%	Not applied	6%	High
*Kyrgyzstan[9]	Convenience	100%	100%	27%	0%	WHO 2013	100%	Not applied	100%	Moderate
*South Africa[10]	Census	0%	0%	20%	12%	WHO 2013	100%	94%	100%	Moderate

For methodological details see: Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JW, et al. "Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis." Lancet 2018; 392 (10150): 821-34. 2018 Sep 1.

* Studies identified through WHO public call for data.

[†] *Census* if all patients treated with shorter regimens at centre or in study provided in database; *Convenience* if neither census or random sample & uncertain on representativeness of the sample of patients provided.

[¶] Participation rate is the number of patients on shorter regimen treatment provided in datasets by investigators divided by the total number of patients treated with the shorter regimen at their centre during the study period, expressed as a percentage.

[ø] All studies received full point for Outcome definitions as they were judged similar to WHO 2013.

[††] For HIV, quality judged adequate despite low rate of testing in Bangladesh, Uzbekistan, Tajikistan, and Kyrgyzstan, given low HIV prevalence settings.

Each quality criteria counts for 1 point, with the exception of % Lost where 2 points are given if ≤ 10%, 1 point if between 10% and 20%, and 0 points if > 20%.
High = 2 points from critical criteria (Sampling method Census/Random; ≥ 80% of patients with DST on either a fluoroquinolone or second-line injectable) + 5 points from other criteria; **Moderate** = 1 point from critical criteria (Sampling method Census/Random; ≥ 80% of patients with DST on either a fluoroquinolone or second-line injectable) + 5 points from other criteria; or 2 from critical + 4 from other; **Low** = not meeting criteria for High or Moderate.

Appendix Table A2b.

Contact person	Sampling method	Info on DST-SLI	Info on DST-FQN	Participation rate	Lost to follow-up rate	Outcome definition	Info on age	Info on HIV	Info on TB Tx history	Quality
Ahuja[11]	Random	92·4%	92·4%	100%	19·0%	Laserson	100%	80·0%	100%	High
Anderson[12]	Census	100%	100%	100%	12·4%	Neither Laserson/WHO	100%	100%	90·5%	High
*Fox [13]	Census	93·1%	96·6%	100%	3·4%	WHO 2013	100%	100%	100%	High
Bang[14]	Census	96·6%	93·1%	96·7%	17·2%	Laserson	100%	100%	100%	High
Barry/Flood (Calif)[15]	Unclear	98·4%	95·2%	100%	4·8%	WHO 2013	98·4%	100%	100%	Moderate
Bonnet[16]	Census	93·3%	93·3%	100%	41·3%	Laserson	100%	11·5%	98·6%	High
*Rodrigues [17]	Census	87%	85%	100%	10%	Laserson	100%	98%	100%	High
Brode[18]	Census	100%	100%	100%	0·0%	Laserson	100%	100%	100%	High
Cegielski[19,20]	Census	92·8%	92·2%	60·1%	19·8%	Laserson	100%	68·3%	98·2%	High
Chan[21]	Census	100%	100%	100%	26·7%	Laserson	100%	80·0%	100%	High
*endTB [22]	Census	95·2%	95·2%	100%	17·5%	Laserson/WHO	100%	100%	100%	High
Guglielmetti[23,24]	Census	100%	100%	100%	11·1%	WHO 2013	100%	100%	100%	High
Isaakidis[25,26]	Census	96·7%	95·4%	100%	11·8%	Laserson	100%	100%	98·0%	High
Jarlsberg[27]	Census	96·4%	96·4%	100%	3·6%	Laserson	100%	92·9%	100·%	High
Kempker[28]	Census	100%	100%	94·9%	32·7%	Laserson	100%	94·7%	100%	High
Koenig[29]	Census	96·3%	93·3%	100%	6·1%	Laserson	99·4%	100%	100%	High
Koh[30,31]	Census	100%	100%	100%	13·4%	WHO 2013	100%	100%	100%	High
Lange[32]	Census	94·0%	96·7%	100%	20·1%	Laserson	100%	99·5%	98·4%	High
Laniado-Laborin[33]	Census	100%	100%	100%	13·5%	Laserson	100%	100%	100%	High
*Kuksa [34]	Census	100%	100%	100%	15%	Laserson	100%	100%	100%	High
*Barkane [35]	Census	100%	100%	100%	15·6%	Laserson	100%	100%	100%	High
Leung[36,37]	Census	100%	100%	100%	19·9%	Laserson	100%	100%	100%	High
Marks[38]	Random	92·3%	91·5%	100%	12·3%	Neither Laserson/WHO	100%	85·4%	100%	High
Migliori[39,40]	Census	96·6%	96·6%	Unclear	10·9%	WHO 2013	100%	98·1%	99·3%	High
Migliori [41]	Census	97·0%	100%	Unclear	3·7%	WHO 2013	100%	99·3%	100%	High
Milanov[42]	Census	94·0%	94·0%	100%	2·0%	Laserson	100%	100%	100%	High
*Ndjeka [43]	Census	100%	100%	100%	18·5%	Laserson/WHO	100%	100%	100%	High
Ndjeka[44]	Unclear	78·2%	81·2%	Unclear	21·1%	Laserson	100%	95·5%	0·0%	Low
Podewils[45]	Census	91·0%	91·2%	100%	15·2%	Laserson	100%	55·6%	100%	High
Riekstina/Leimane[46]	Census	100%	100%	100%	14·7%	Laserson	100%	94·0%	100%	High
*Seo [47]	Census	100%	100%	100%	16%	Laserson	100%	100%	100%	High
Shim[31,48]	Census	100%	100%	86·4%	8·2%	WHO 2013	100%	40%	100%	High
Smith[49]	Census	100%	100%	100%	21·5%	Laserson	100%	100%	98·5%	High
TMC207-C208[50,51]	RCT	84·8%	84·8%	82·5%	28·8%	Laserson	100%	100%	100%	High
TMC207-C209[52]	Census	76·1%	76·1%	93·1%	15·2%	Laserson	100%	96·5%	100%	Moderate
van der Werf[53]	Census	100%	98·2%	100%	13·4%	Laserson	100%	92·0%	96·4%	High
*Vasilyeva [54]	Census	94·4%	94·4%	100%	16%	WHO 2013	100%	100%	100%	High
*Viiklepp[55]	Census	100%	100%	100%	11·7%	Laserson	100·%	99·7%	100%	High
Yim/Kwak[56]	Census	100%	100%	100%	4·9%	WHO 2013	100%	100%	100%	High

For methodological details see: Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JW, et al. "Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis." Lancet 2018; 392 (10150): 821-34. 2018 Sep 1.

* Studies identified through WHO public call for data.

Appendix Table A3: Associations between drug-susceptibility test results for pyrazinamide (Pza), ethambutol (Emb), and pro/ethionamide (Pto/Eto)

Table A3a: Pyrazinamide and ethambutol resistance (R) & susceptibility (S)

	Emb-R	**Emb-S**	**Total**
Pza-R	459 (74% of Pza-R) (54% of Emb-R)	159 (26% of Pza-R) (32% of Emb-S)	618
Pza-S	397 (54% of Pza-S) (46% of Emb-R)	344 (46% of Pza-S) (68% of Emb-S)	741
Total	856	503	*Fisher's p-value for table <.001*

Table A3b: Pyrazinamide and pro/ethionamide susceptibility

	Pto/Eto-R	**Pto/Eto -S**	**Total**
Pza-R	127 (24% of Pza-R) (51% of Pto/Eto-R)	401 (76% of Pza-R) (43% of Pto/Eto -S)	528
Pza-S	124 (19% of Pza-S) (49% of Pto/Eto -R)	520 (81% of Pza-S) (57% of Pto/Eto -S)	644
Total	251	621	*Fisher's p-value for table =·05*

Table A3c: Ethambutol and pro/ethionamide susceptibility

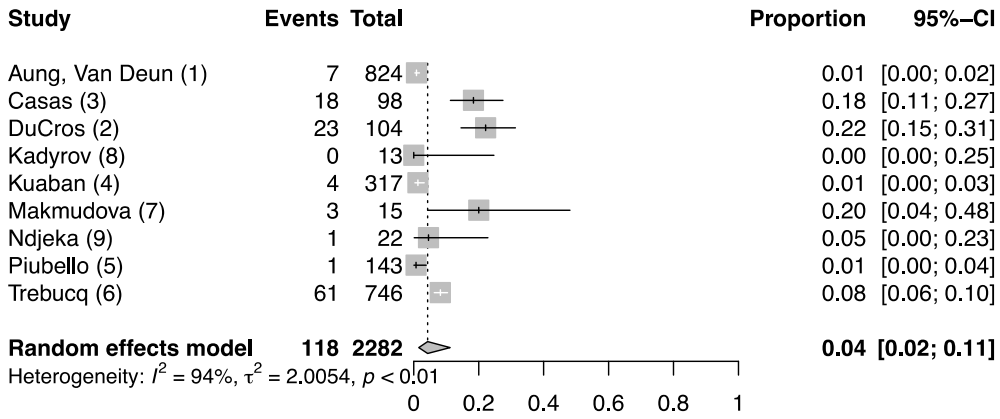
	Pto/Eto -R	**Pto/Eto -S**	**Total**
Emb-R	270 (22% of Emb-R) (68% of Pto/Eto-R)	981 (78% of Emb-R) (63% of Pto/Eto-S)	1251
Emb-S	125 (18% of Emb-S) (32% of Pto/Eto-R)	586 (82% of Emb-R) (37% of Pto/Eto-S)	711
Total	395	1567	*Fisher's p-value for table =·04*

Table A3d: Correlation between pyrazinamide, ethambutol, and pro/ethionamide resistance in patients tested for all 3

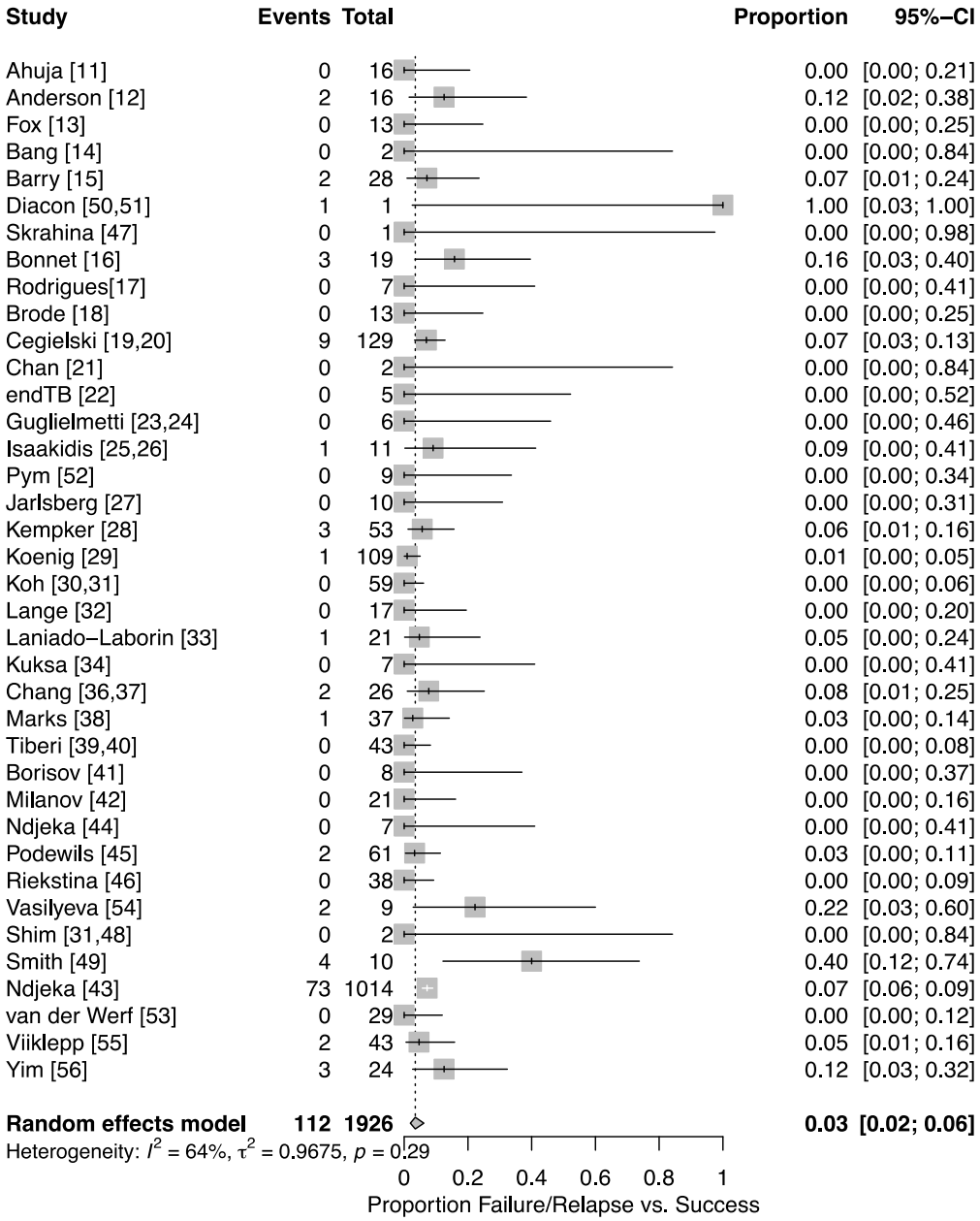
	Emb-R	**Pto/Eto -R**
Pza-R	ρ = 0·22 p-value <·0001	ρ = 0·07 p-value=0·02
Emb-R	--	ρ = 0·04 p-value=0·16

Appendix Figure A2. Proportion of Failure/Relapse vs. Success, comparing shorter & longer MDR-TB regimens

A) Shorter

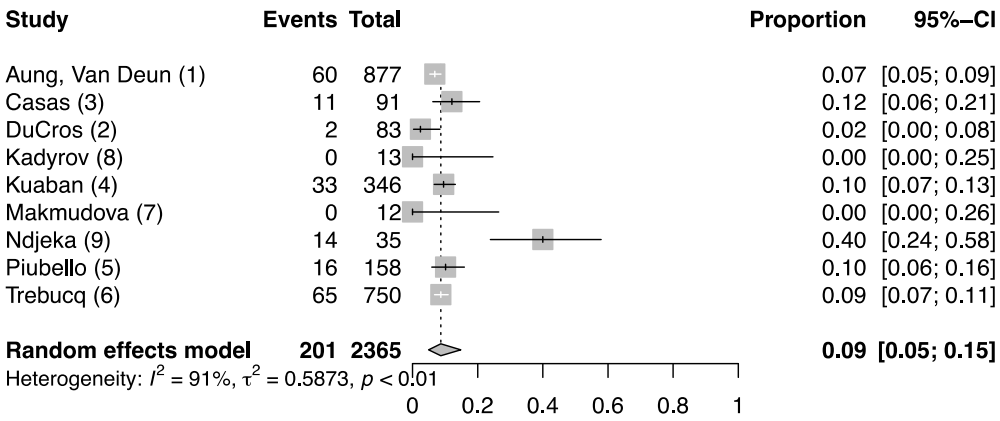


B) Longer

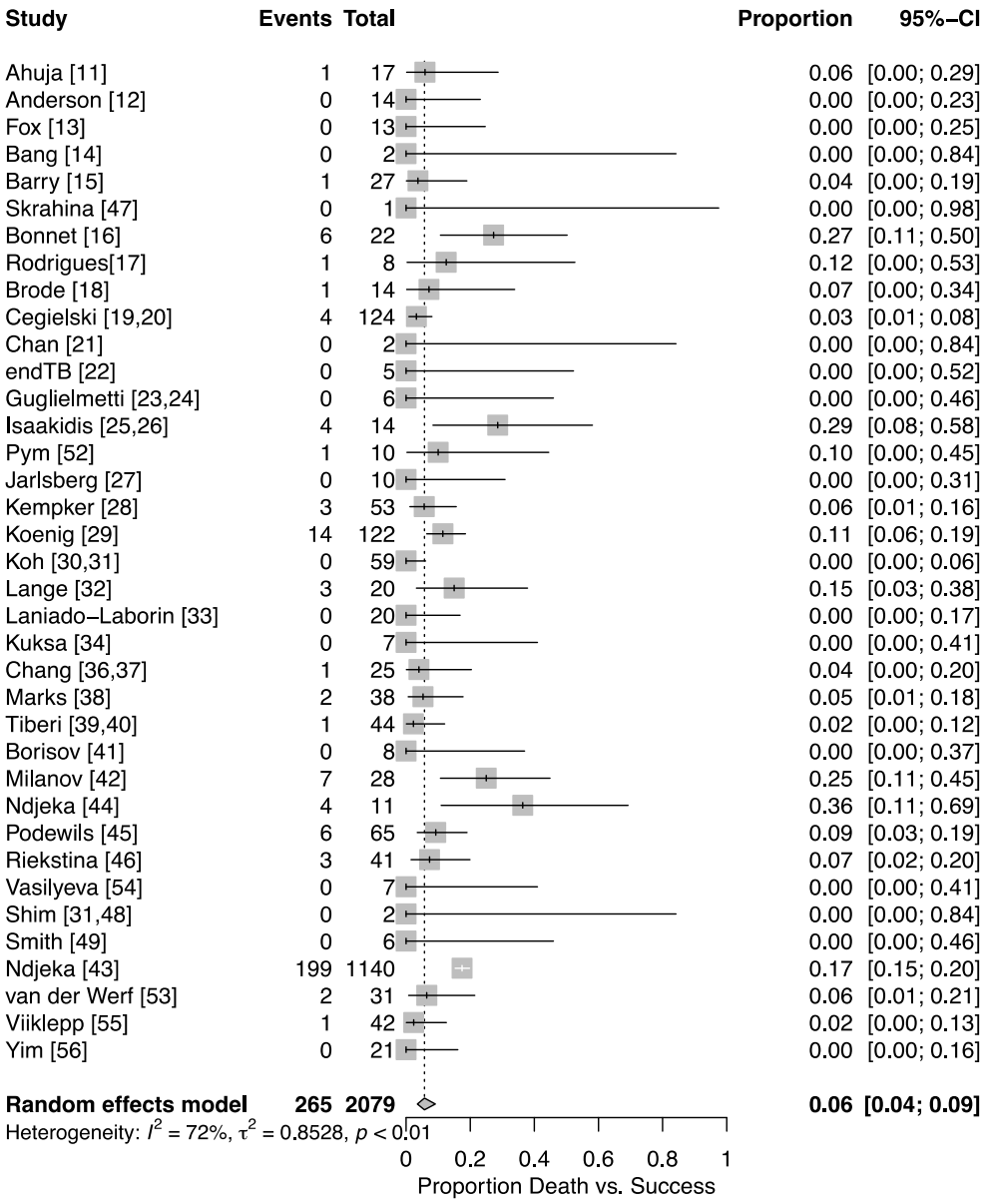


Appendix Figure A3. Proportion of Death vs. Success, comparing shorter & longer MDR-TB regimens

A) Shorter

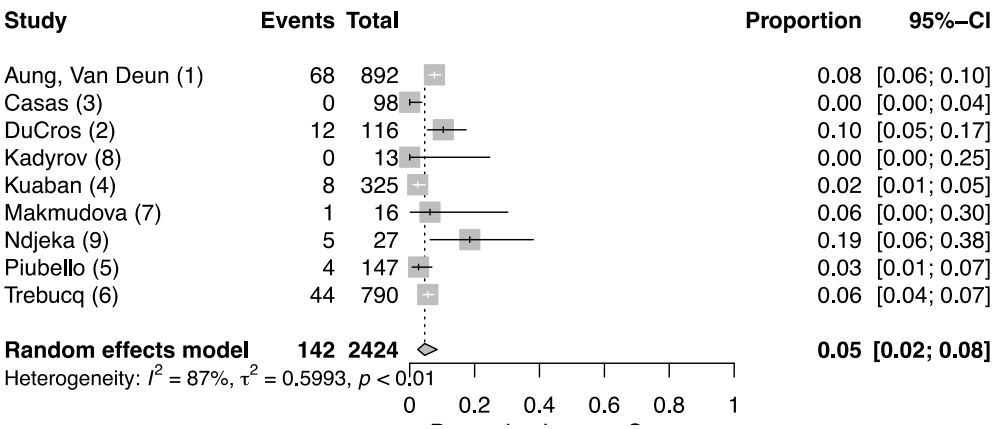


B) Longer

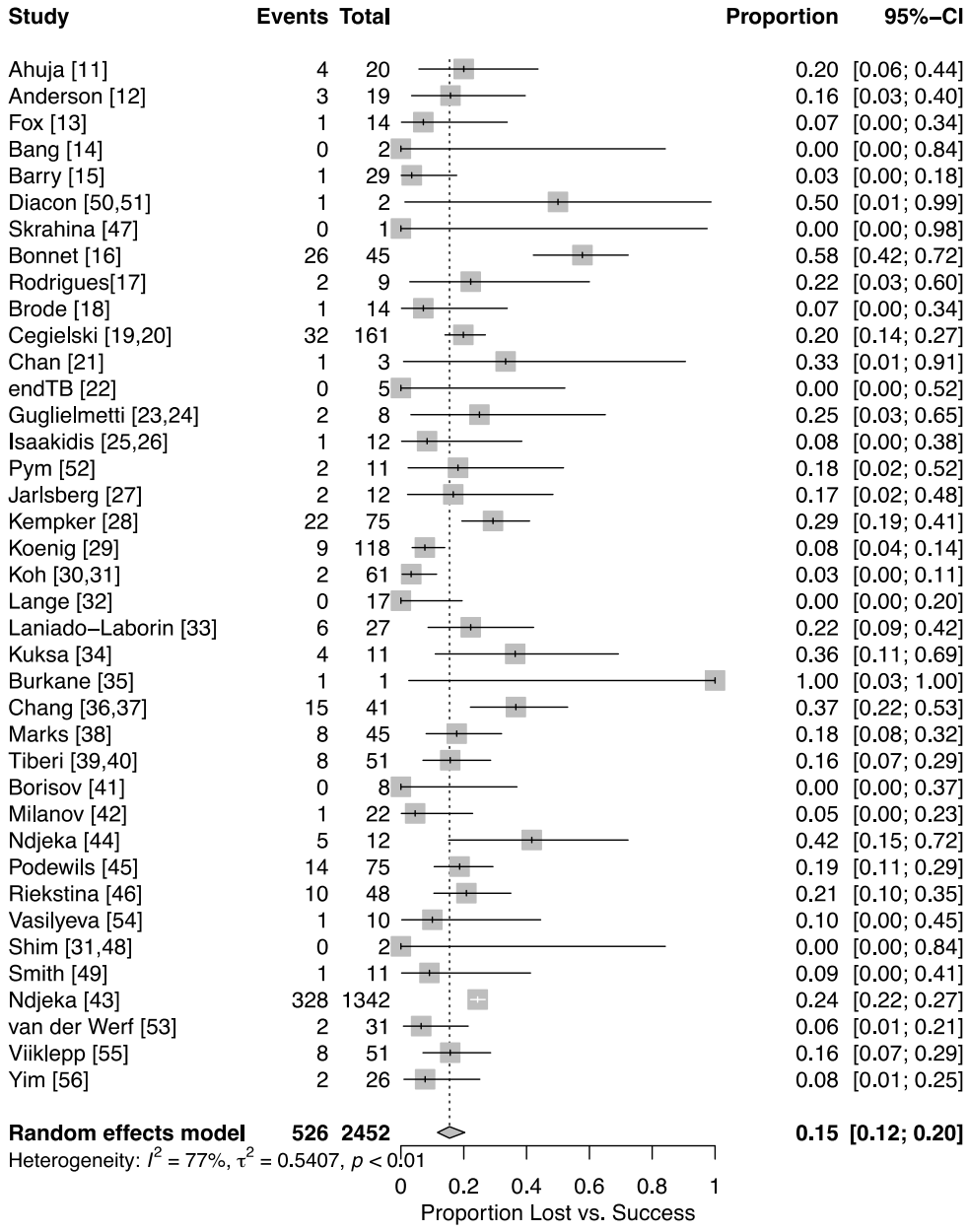

Study
Events
Total
Proportion
95%–CI
Ahuja [11] 1 17 0.06 [0.00; 0.29]
Anderson [12] 0 14 0.00 [0.00; 0.23]
Fox [13] 0 13 0.00 [0.00; 0.25]
Bang [14] 0 2 0.00 [0.00; 0.84]
Barry [15] 1 27 0.04 [0.00; 0.19]
Skrahina [47] 0 1 0.00 [0.00; 0.98]
Bonnet [16] 6 22 0.27 [0.11; 0.50]
Rodrigues[17] 1 8 0.12 [0.00; 0.53]
Brode [18] 1 14 0.07 [0.00; 0.34]
Cegielski [19,20] 4 124 0.03 [0.01; 0.08]
Chan [21] 0 2 0.00 [0.00; 0.84]
endTB [22] 0 5 0.00 [0.00; 0.52]
Guglielmetti [23,24] 0 6 0.00 [0.00; 0.46]
Isaakidis [25,26] 4 14 0.29 [0.08; 0.58]
Pym [52] 1 10 0.10 [0.00; 0.45]
Jarlsberg [27] 0 10 0.00 [0.00; 0.31]
Kempker [28] 3 53 0.06 [0.01; 0.16]
Koenig [29] 14 122 0.11 [0.06; 0.19]
Koh [30,31] 0 59 0.00 [0.00; 0.06]
Lange [32] 3 20 0.15 [0.03; 0.38]
Laniado–Laborin [33] 0 20 0.00 [0.00; 0.17]
Kuksa [34] 0 7 0.00 [0.00; 0.41]
Chang [36,37] 1 25 0.04 [0.00; 0.20]
Marks [38] 2 38 0.05 [0.01; 0.18]
Tiberi [39,40] 1 44 0.02 [0.00; 0.12]
Borisov [41] 0 8 0.00 [0.00; 0.37]
Milanov [42] 7 28 0.25 [0.11; 0.45]
Ndjeka [44] 4 11 0.36 [0.11; 0.69]
Podewils [45] 6 65 0.09 [0.03; 0.19]
Riekstina [46] 3 41 0.07 [0.02; 0.20]
Vasilyeva [54] 0 7 0.00 [0.00; 0.41]
Shim [31,48] 0 2 0.00 [0.00; 0.84]
Smith [49] 0 6 0.00 [0.00; 0.46]
Ndjeka [43] 199 1140 0.17 [0.15; 0.20]
van der Werf [53] 2 31 0.06 [0.01; 0.21]
Viiklepp [55] 1 42 0.02 [0.00; 0.13]
Yim [56] 0 21 0.00 [0.00; 0.16]
Random effects model 265 2079 0.06 [0.04; 0.09]
Heterogeneity: I^2 = 72%, τ^2 = 0.8528, p < 0.01
0
0.2
0.4
0.6
0.8
1
Proportion Death vs. Success

Appendix Figure A4. Proportion of Lost vs. Success, Failure, or Relapse comparing shorter & longer MDR-TB regimens

A) Shorter



B) Longer



Appendix Table A4: Odds ratios for associations of covariates with outcomes, using univariable individual patient-data meta-regression

Covariates	Odds ratio (95%CI)		
	Fail/relapse vs Success	**Death vs Success**	**Loss to follow-up vs Success, Failure, Relapse**
Age (per 1 year older)	1·0 (0·99-1·01)	**1·04 (1·03-1·05)**	1·0 (0·99-1·01)
Sex (reference: female)	1·0 (0·7-1·3)	1·0 (0·8-1·2)	**1·5 (1·3-1·8)**
PLWH (reference: HIV negative people)	1·1 (0·8-1·6)	**2·8 (2·1-3·6)**	1·0 (0·8-1·3)
Extensive disease (reference: not extensive)	**1·4 (0·98-2)**	1·1 (0·9-1·4)	1·1 (0·9-1·3)
Prior treatment with first-line drugs (reference: no prior treatment)	1·0 (0·8-1·4)	**1·3 (1·0-1·6)**	**1·3 (1·04-1·5)**
Pyrazinamide resistance (reference: sensitive to pyrazinamide)	**1·6 (0·96-2·7)**	1·4 (0·9-2·1)[F]	**0·6 (0·4-0·9)**
Prothionamide[*] resistance (reference: sensitive to prothionamide[*])	1·4 (0·7-2·7)	0·8 (0·5-1·3)	1·0 (0·7-1·5)
Ethambutol resistance (reference: sensitive to ethambutol)	**2·9 (1·6-5·3)**	1·2 (0·9-1·7)	0·8 (0·6-1·1)

Confidence intervals suggestive of increased odds or risk of failure or relapse are in bold red font.
Confidence intervals suggestive of lower odds or risk of failure or relapse are in bold black font.
Data are unadjusted odds ratios (95% CI) from random-effects meta-regression. PLWH: people living with HIV infection.
F: fixed effects model used as random-effects model did not converge.
[*]Or ethionamide.

Appendix Table A5: Comparison of shorter regimens to longer regimens amongst patients with rifampin or multidrug-resistant tuberculosis confirmed susceptible to fluoroquinolones and additionally resistant to at least two of: pyrazinamide, ethambutol, or prothionamide/ethionamide, using individual patient-data meta-analysis

	Studies Shorter, Longer	Shorter Events/ Total	Longer Events/ Total	Propensity score matched multivariable meta-regression		
				N Pairs	aOR (95%CI)	aRD (95% CI)
Fail/relapse vs Success	7, 27	31/244	13/324	244	**5·2 (1·5, 17·6)**[F]	**0·10 (0·05, 0·15)**
Death during first 12 months of treatment vs Success	6, 24	14/227	27/338	227	0·4 (0·1, 1·9)	-0·03 (-0·09, 0·03)
Lost vs Success, Fail/relapse	7, 24	13/257	53/377	257	0·2 (0·0, 1·8)	**-0·08 (-0·14, -0·02)**

All models adjust for age, sex, HIV status, previous treatment with first-line tuberculosis medications, and extensiveness of disease. Results were adjusted as described in the Methods. aOR: adjusted odds ratio; aRD: adjusted risk difference.
F: fixed effects model used as random-effects model did not converge.

Appendix Table A6: Characteristics of patients included in the comparison of moxifloxacin- or levofloxacin-based shorter regimens with longer regimens composed per 2018 World Health Organization guidelines including either bedaquiline or linezolid

	Shorter, n=1004	**Longer, n=162**
Baseline characteristics	1004	162
Mean Age (standard deviation)	35·5 (12·8)	39·2 (13·2)
Male Sex	594 (59·2%)	96 (59·3%)
People living with HIV	204 (20·4%)	93 (57·4%)
Antiretroviral treatment	175 (90·2%)	93 (100%)
Extensive disease	834 (83·1%)	131 (80·9%)
Previous Treatment with First Line Drugs	780 (82·5%)	73 (45·9%)
High Income Country	0 (0%)	12 (7·4%)
Upper Middle Income Country	41 (4·1%)	149 (92%)
Low Middle or Low Income Country	963 (95·9%)	1 (0·6%)
Pyrazinamide-resistant tuberculosis	226 (59%)	17 (77·3%)
Ethambutol-resistant tuberculosis	224 (67·3%)	18 (78·3%)
Ethionamide/Prothionamide-resistant tuberculosis	156 (50·2%)	13 (61·9%)
Total number of drugs in regimen, median (IQR)	7	7 (6-8)*
WHO 2018 Group A Drugs in regimen		
Moxifloxacin or levofloxacin	1004 (100%)	162 (100%)
Bedaquiline	0	151(93·2%)
Linezolid	0	144(88·9%)
WHO 2018 Group B Drugs in regimen		
Cycloserine	0	16(9·9%)
Clofazimine	1004 (100%)	122(75·3%)

Restricted to patients with tuberculosis confirmed susceptible to fluoroquinolones.
*This is the number of drugs given for > 1 month, not all of which may have been given concomitantly.

Appendix Table A7A. Sensitivity Analysis: Comparison of shorter regimens to longer regimens amongst patients with rifampin-resistant and isoniazid-susceptible tuberculosis, rifampin-resistant tuberculosis with unmeasured DST for isoniazid, or multidrug-resistant tuberculosis, using individual patient-data meta-analysis

	Studies Shorter, Longer	Shorter Events/ Total	Longer Events/ Total	Propensity score matched multivariable meta-regression		
				N Pairs	aOR (95%CI)	aRD (95% CI)
(A) Including patients with INH-susceptible, RR-TB						
Fail/relapse vs Success	9, 38	123/2478	115/1953	1953	1·5 (0·8, 3·0)	0·02 (-0·01, 0·04)
Death vs Success	9, 37	225/2580	268/2106	2106	1·2 (0·96, 1·5)	0·02 (-0·01, 0·05)
Lost vs Success, Fail/relapse	9, 39	149/2627	533/2486	2486	0·2 (0·2, 0·3)	-0·15 (-0·17, -0·13)

All models adjust for age, sex, HIV status, previous treatment with first-line tuberculosis medications, and extensiveness of disease. Results were adjusted as described in the Methods. aOR: adjusted odds ratio; aRD: adjusted risk difference.

Appendix Table A7B. Sensitivity Analysis: Comparison of shorter regimens to longer regimens amongst patients with rifampin- or multidrug-resistant tuberculosis confirmed resistant to fluoroquinolones, using individual patient-data meta-analysis

	Studies Shorter, Longer	Shorter Events/ Total	Longer Events/ Total	Propensity score matched multivariable meta-regression		
				N Pairs	aOR (95%CI)	aRD (95% CI)
(B) Fluoroquinolone-resistant						
Fail/relapse vs Success	4, 15	39/103	10/130	103	15·0 (2·8, 80·6)	0·33 (0·22, 0·44)
Death vs Success	4, 16	8/72	14/134	72	2·1 (0·3, 17·0)	0·04 (-0·08, 0·15)
Lost vs Success, Fail/relapse	4, 17	8/111	37/167	111	0·3 (0·1, 1·4)	-0·11 (-0·25, 0·03)

All models adjust for age, sex, HIV status, previous treatment with first-line tuberculosis medications, and extensiveness of disease. Results were adjusted as described in the Methods. aOR: adjusted odds ratio; aRD: adjusted risk difference.

References for Appendix

1. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis* 2014; **18**(10): 1180-7.
2. Van Deun A, Maug AK, Hamid Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Resp Crit Care Med* 2010; **182**(5): 684-92.
3. Médecins Sans Frontières Manson Unit, Ministry of Health Uzbekistan. Unpublished data. 2018.
4. Médecins Sans Frontières Operational Center Amsterdam, MSF-OCA Swaziland, Ministry of Health Swaziland. Unpublished data. 2018.
5. Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Abena Foe JL, Trebucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis* 2015; **19**(5): 517-24.
6. Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis* 2014; **18**(10): 1188-94.
7. Trebucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis* 2018; **22**(1): 17-25.
8. Republic of Tajikistan TB Centre and KNCV. Unpublished data. 2018.
9. Kyrgyz Republic and KNCV. Unpublished data. 2018.
10. South African Ministry of Health. Unpublished Data. 2018.
11. Anger HA, Dworkin F, Sharma S, Munsiff SS, Nilsen DM, Ahuja SD. Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, New York City, 2000-06. *J Antimicrob Chemother* 2010; **65**(4): 775-83.
12. Anderson LF, Tamne S, Watson JP, et al. Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007. *Euro Surveill* 2013; **18**(40).
13. Fox G. Unpublished data (Australia). 2018.
14. Bang DL, T.; Thomsen, V. O.; Andersen, A. B. Multidrug-resistant tuberculosis: Treatment outcome in Denmark, 1992-2007. *Scand J Infect Dis* 2010; **42**(4): 288-93.
15. Barry PM, Flood J, Lowenthal P, Westenhouse J, California Department of Public Health. Unpublished data (California, USA). 2016.
16. Bonnet M, Pardini M, Meacci F, et al. Treatment of tuberculosis in a region with high drug resistance: outcomes, drug resistance amplification and re-infection. *PLoS ONE* 2011; **6**(8): e23081.
17. Rodrigues. Unpublished data (Brazil). 2018.
18. Brode S, West Park Healthcare Centre. Unpublished data (Toronto, Canada). 2016.
19. Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial Versus Acquired Second-Line Drug Resistance. *Clin Infect Dis* 2016; **62**(4): 418-30.
20. Yuen CM, Kurbatova EV, Tupasi T, et al. Association between Regimen Composition and Treatment Response in Patients with Multidrug-Resistant Tuberculosis: A Prospective Cohort Study. *PLoS Med* 2015; **12**(12): e1001932.
21. Chan ED, National Jewish Health. Unpublished data (Denver, USA). 2016.
22. endTB investigators. Unpublished data. 2018.
23. Guglielmetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Respir J* 2017; **49**(3).
24. Guglielmetti L, Le Du D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; **60**(2): 188-94.
25. Isaakidis P, Varghese B, Mansoor H, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. *PLoS ONE* 2012; **7**(7): e40781.
26. Hughes J, Isaakidis P, Andries A, et al. Linezolid for multidrug-resistant tuberculosis in HIV-infected and -uninfected patients. *Eur Respir J* 2015; **46**(1): 271-4.
27. Jarlsberg L, Nahid P. Unpublished data (San Francisco, USA). 2016.
28. Kempker RR, Kipiani M, Mirtskhulava V, Tukvadze N, Magee MJ, Blumberg HM. Acquired Drug Resistance in Mycobacterium tuberculosis and Poor Outcomes among Patients with Multidrug-Resistant Tuberculosis. *Emerg Infect Dis* 2015; **21**(6): 992-1001.
29. Charles M, Vilbrun SC, Koenig SP, et al. Treatment outcomes for patients with multidrug-resistant tuberculosis in post-earthquake Port-au-Prince, Haiti. *Am J Trop Med Hyg* 2014; **91**(4): 715-21.
30. Jeong BH, Jeon K, Park HY, et al. Outcomes of pulmonary MDR-TB: impacts of fluoroquinolone resistance and linezolid treatment. *J Antimicrob Chemother* 2015; **70**(11): 3127-33.
31. Koh WJ, Kang YR, Jeon K, et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; **67**(6): 1503-7.

32. Eker B, Ortmann J, Migliori GB, et al. Multidrug- and extensively drug-resistant tuberculosis, Germany. *Emerg Infect Dis* 2008; **14**(11): 1700-6.
33. Laniado-Laborin R, Estrada-Guzman J, Perez H, Batiz-Armenta F, Alcantar-Schramm JM. Treatment of multidrug-resistant tuberculosis in a high-prevalence region through a binational consortium. *Int J Tuberc Lung Dis* 2012; **16**(5): 610-1.
34. Kuksa L. Unpublished data (Latvia). 2018.
35. Barkane. Unpublished data (Latvia, Delamanid). 2018.
36. Chang KC, Yew WW, Cheung SW, et al. Can intermittent dosing optimize prolonged linezolid treatment of difficult multidrug-resistant tuberculosis? *Antimicrob Agents Chemother* 2013; **57**(7): 3445-9.
37. Chang KC, Leung CC, Yew WW, et al. Pyrazinamide may improve fluoroquinolone-based treatment of multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2012; **56**(11): 5465-75.
38. Marks SM, Flood J, Seaworth B, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005-2007. *Emerg Infect Dis* 2014; **20**(5): 812-21.
39. Tiberi S, Payen MC, Sotgiu G, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; **47**(4): 1235-43.
40. Tiberi S, Sotgiu G, D'Ambrosio L, et al. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; **47**(6): 1758-66.
41. Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017; **49**(5).
42. Milanov V, Falzon D, Zamfirova M, et al. Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria, 2009-2010. *International journal of mycobacteriology* 2015; **4**(2): 131-7.
43. Ndjeka N. Unpublished data (South Africa). 2018.
44. Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *Int J Tuberc Lung Dis* 2015; **19**(8): 979-85.
45. Podewils LJ, Gler MT, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS ONE* 2013; **8**(7): e70064.
46. Riekstina V, Leimane V, Cirule A, Kuksa L, Latvia National TB registry. Unpublished data (Latvia). 2016.
47. Skrahina A. Unpublished data (Belarus). 2018.
48. Jo KW, Lee SD, Kim WS, Kim DS, Shim TS. Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2014; **18**(1): 39-43.
49. Smith SE, Ershova J, Vlasova N, et al. Risk factors for acquisition of drug resistance during multidrug-resistant tuberculosis treatment, Arkhangelsk Oblast, Russia, 2005-2010. *Emerg Infect Dis* 2015; **21**(6): 1002-11.
50. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; **371**(8): 723-32.
51. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; **360**(23): 2397-405.
52. Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J* 2016; **47**(2): 564-74.
53. van Altena R, de Vries G, Haar CH, et al. Highly successful treatment outcome of multidrug-resistant tuberculosis in the Netherlands, 2000-2009. *Int J Tuberc Lung Dis* 2015; **19**(4): 406-12.
54. Vasilyeva I. Unpublished data (Russia). 2018.
55. Viiklepp P, Estonian TB Registry. Unpublished data (Estonia). 2016.
56. Kwak N, Kim HR, Yoo CG, Kim YW, Han SK, Yim JJ. Changes in treatment outcomes of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2015; **19**(5): 525-30.