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How to cite

ROELENS, Maroussia et al. Evidence-based Definition for Extensively Drug-resistant Tuberculosis. In: American Journal of Respiratory and Critical Care Medicine, 2021, vol. 204, n° 6, p. 713–722. doi: 10.1164/rccm.202009-3527OC

This publication URL: https://archive-ouverte.unige.ch/unige:155191

Publication DOI: 10.1164/rccm.202009-3527OC

Evidence-based Definition for Extensively Drug-resistant Tuberculosis

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AJRCCM Articles in Press. Published June 09, 2021 as 10.1164/rccm.202009-3527OC

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AJRCCM Articles in Press. Published June 09, 2021 as 10.1164/rccm.202009-3527OC

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Funding: M. Roelens and O. Keiser were funded by the Swiss National Science Foundation SNF (grant no 163878). C. Lange is supported by the German Centre of Infection Research (DZIF).

Running title: Definition for extensively drug-resistant TB

Subject category: 11.02 Epidemiology of Tuberculosis

Word count: 3544

At a Glance

Scientific Knowledge on the Subject:

Since 2006 and until 2020, extensively drug-resistant tuberculosis (XDR-TB) was defined as multidrug-resistant tuberculosis (MDR-TB) with additional resistance to any fluoroquinolones and any second-line injectable drugs (SLID). This definition may have lost clinical relevance after WHO introduced its new treatment recommendations in 2019 that downgraded SLID role, but a clinically significant evidence for an updated definition is still lacking.

What This Study Adds to the Field:

Our study assessed the association between unfavourable treatment outcome in MDR-TB patients with bacilli resistance to fluoroquinolones and SLID, and the use of the WHO Group A drugs. The results of the study contributed to, and support, the updated definition of XDR-TB as MDR-TB plus additional resistance to any fluoroquinolones and either linezolid or bedaquiline, and the new definition of pre-XDR-TB as MDR-TB plus additional resistance to any fluoroquinolone.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

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Abstract

Rationale: Until 2020, extensively drug-resistant tuberculosis (XDR-TB) was defined as resistance to rifampicin and isoniazid (multidrug-resistant tuberculosis, MDR-TB), any fluoroquinolone (FQ) and any second-line injectable drug (SLID). In 2019 the World Health Organization issued new recommendations for managing patients with drug-resistant tuberculosis, substantially limiting the role of SLID in MDR-TB treatment and thus putting that XDR-TB definition into question.

Objective: To propose an up-to-date definition for XDR-TB.

Methods: We used a large dataset to assess treatment outcomes for MDR-TB patients exposed to any type of longer regimen. We included patients with bacteriologically confirmed MDR-TB and known FQ and SLID resistance results. We did logistic regression to estimate adjusted odds ratios (aORs) for unfavourable treatment outcome (failure, relapse, death, loss-to-follow-up) by resistance pattern (FQ, SLID) and Group A drug use (moxifloxacin/levofloxacin, linezolid, bedaquiline).

Measurements and Main Results: We included 11,666 patients with MDR-TB; 4653 (39.9%) had an unfavourable treatment outcome. Resistance to FQs increased the odds of an unfavourable treatment outcome (aOR 1.91; 95% confidence interval [95%CI] 1.63-2.23). Administration of bedaquiline and/or linezolid improved treatment outcomes regardless of resistance to FQ and/or SLID. Among XDR-TB patients, compared to persons receiving no Group A drug, aORs for unfavourable outcome were 0.37 (95%CI 0.20-0.69) with linezolid only, 0.40 (95%CI 0.21-0.77) with bedaquiline only, and 0.21 (95%CI 0.12-0.38) with both.

Conclusions: Our study supports a new definition of XDR-TB as MDR plus additional resistance to FQ plus bedaquiline and/or linezolid, and helps assess the adequacy of this definition for surveillance and treatment choice.

Word count (abstract): 249; **Keywords:** tuberculosis, drug resistance, meta-analysis, epidemiology

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Introduction

Globally, drug-resistant tuberculosis is a public health crisis. The World Health Organization (WHO) estimated that in 2018, nearly 500,000 persons developed rifampicin-resistant tuberculosis (RR-TB) worldwide, of whom over 80% had multidrug-resistant tuberculosis (MDR-TB), defined as disease caused by *Mycobacterium tuberculosis* strains resistant to at least rifampicin and isoniazid (1). Treatment success for MDR/RR-TB remains low, around 56% (1), with 11% of patients dying (2).

Of all patients estimated to have developed MDR-TB in 2018, 6.2% (95% confidence interval [CI]: 4.4–8.2%) had extensively drug-resistant tuberculosis (XDR-TB) (1), defined since 2006 as MDR-TB with additional *M. tuberculosis* resistance to any fluoroquinolone (FQ) and any of the three second-line injectable drugs (SLIDs) (amikacin, capreomycin or kanamycin). The XDR-TB definition is important for surveillance and statistical purposes, but has also implications for prognosis. The WHO reports overall treatment success as low as 39% for patients with XDR-TB (1).

A comparative analysis of the treatment outcomes conducted in the first large individual patient data meta-analysis (IPDMA) including more than 10,000 patients with MDR-TB (3,4) demonstrated a treatment success of 64% in patients with MDR-TB "*sensu stricto*" (i.e. without additional resistance to FQs or SLIDs) and 40% in patients with XDR-TB (4). Among patients with "pre-XDR-TB" (an unofficial definition of MDR-TB with additional resistance to either any FQ or any SLID (5)), treatment success was higher among those with resistance to SLID (56%, 95% CI 45-66%) than those with resistance to FQ (48%, 95% CI 36-60%). Another analysis showed that further sub-categories of XDR-TB had treatment success rates comparable to the pre-antibiotic era, the lowest being 19% when the *M. tuberculosis* strains had additional resistance to all SLIDs, all older second-line drugs (SLDs; ethionamide/prothionamide, p-aminosalicylic acid [PAS], cycloserine), ethambutol and pyrazinamide (3,6).

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In March 2019, WHO updated its MDR/RR-TB treatment guidelines informed primarily by an updated IPDMA of MDR/RR-TB data from 38 countries (7,8). An update of those guidelines was released in June 2020 (9). The aim of that IPDMA analysis was to investigate the association between treatment success and individual TB drugs. MDR/RR-TB treatment success was significantly higher with the use of linezolid, moxifoxacin, levofloxacin, bedaquiline, clofazimine, and carbapenems, although survival benefit was only observed with FQs, bedaquiline and linezolid. By contrast, among SLIDs, only amikacin had a positive effect on treatment success: capreomycin and kanamycin were associated with worse treatment outcomes.

As a result, WHO reclassified the medicines for MDR/RR-TB treatment in longer regimens into Group A (levofloxacin/moxifloxacin, bedaquiline, linezolid), Group B (clofazimine, cycloserine/terizidone) and Group C (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin/meropenem, amikacin/streptomycin, ethionamide/prothionamide, PAS), and recommended that, where possible, regimens be composed of all three Group A agents and at least one Group B agent, so that treatment starts with at least four medicines likely to be effective. If only one or two Group A agents can be used, both Group B agents should be included and if the regimen cannot be composed with agents from Groups A and B alone, Group C agents are to be added (8).

With these new guidelines, the 2006 XDR-TB definition may have lost clinical relevance as bedaquiline is now included in most MDR/RR-TB treatment regimens and treatment with SLIDs has become an exception (9-11). Potential new definitions have been proposed based on MDR/RR-TB with resistance to FQs and at least one other Group A drug (5,12,13), but clinical evidence for these definitions is lacking.

The aim of the present study was to assess the associations between the use of anti-TB drugs in treatment regimens and unfavourable treatment response to propose up-to-date definitions for XDR-TB and explore a formal definition of “pre-XDR-TB“. We assessed treatment outcomes for MDR-TB

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patients exposed to any type of longer regimen, and investigated the effect of the use of Group A and B drugs and the type of resistance on treatment outcomes.

Methods

Data source and population

We used the latest version of the IPDMA database (June 2018), following the same inclusion criteria as before (7,14). Detailed description of the IPDMA composition process (centre characteristics, outcome definition, drug susceptibility testing (DST) methods and drug dosages), and each individual study is shown elsewhere (15). The data include anonymised information for 12,938 patients from 38 countries and 52 studies (**Appendix E1**). We included patients with MDR-TB caused by *M. tuberculosis* with confirmed resistance to rifampicin and isoniazid. We excluded patients with TB caused by *M. tuberculosis* susceptible or with unknown resistance to isoniazid (n=887), patients with missing age (n=11) and/or gender (n=2) and patients with missing *M. tuberculosis* DST data for FQ and/or SLID (n=372). Overall, 11,666 individuals were included (**Appendix E1**).

For persons who had multiple MDR-TB tuberculosis treatments in each study, treatment outcome was recorded only for the last complete treatment course. Data included demographic and clinical variables collected at the start of treatment (e.g. age, sex, previous treatment with first-line drugs (FLDs) or SLDs, extent of the tuberculosis disease, HIV), diagnostic information (including DST), TB treatment received (number and duration of prescribed drugs, overall and for the intensive and continuation phase) and treatment outcomes.

Definitions

Treatment outcomes were defined in accordance with the WHO guidelines as explained in detail elsewhere (15,16). They were summarized as unfavourable if the treatment failed, a relapse occurred or the patient died or was lost-to-follow-up; and as favourable in case of cure or completed treatment with no reported failure or relapse (15,16).

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Drug resistance patterns were divided into four groups: MDR-TB "*sensu stricto*", MDR-TB plus resistance to any FQ and no resistance to SLID, MDR-TB plus resistance to any SLID and no resistance to FQ, and XDR-TB according to the 2006 definition. For the purpose of this study, we define "pre-XDR" as MDR plus additional resistance to any FQ or any SLID, but not both.

Statistical analysis

We used multivariate imputation by chained equations (R version 3.6.0, package *mice* version 3.9.0 (17)) to impute missing values for the site of disease (pulmonary tuberculosis with or without extra-pulmonary involvement), HIV and antiretroviral use, and previous treatment history. We also imputed drug susceptibility to ethambutol, pyrazinamide, ethionamide/prothionamide, and PAS. These drugs were considered effective if the patient's strain was known to be, or (in case the information was missing) imputed as, susceptible to the drug. We assumed that bedaquiline, linezolid, clofazimine and cycloserine/terizidone were effective if the DST results indicated susceptibility, or if resistance was not documented (as per WHO guidance). As DST to FQ and SLID was an inclusion criterion, DST was not imputed for these drugs and they were only considered effective if susceptible on DST. We performed ten sampling iterations to generate 20 imputed datasets with all original data preserved, and missing data imputed.

First, we performed logistic regression using generalized linear mixed models (R package *lme4*, version 1.1.23) to assess the association between potentially relevant variables and unfavourable treatment outcome. Each model contained random intercepts for each study to account for clustering. Regression analyses were run on each imputed dataset, and estimates pooled according to Rubin's rules to calculate odds ratios with 95% CI (18).

Univariable analyses were run on the following covariates: drug resistance group (MDR "*sensu stricto*"; MDR+FQ; MDR+SLID; XDR); Group A drug use (none; moxifloxacin/levofloxacin only; bedaquiline with or without moxifloxacin/levofloxacin; linezolid with or without moxifloxacin/levofloxacin; bedaquiline and linezolid with or without moxifloxacin/levofloxacin), Group B drug use (none; clofazimine only;

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cycloserine/terizidone only; both), use of carbapenems (no; yes), number of effective drugs used apart from FQ, SLID, linezolid, bedaquiline, clofazimine, cycloserine/terizidone and carbapenems (0; 1; ≥2), prior TB treatment (none; FLD only; any SLD), age in years (≤25; 26-45; >45), gender, HIV status (HIV-negative; HIV-positive without antiretroviral therapy (ART); HIV-positive with any combination ART), country income level (low/lower-middle; upper-middle; high) based on the World Bank 2018 classification (19), year of treatment initiation (≤2003, 2004-2008, 2009-2012, 2013-2016), and presence of extensive tuberculosis disease (no; yes)—defined as having at least one of these characteristics: positive acid-fast bacilli (AFB) smear status or presence of cavitation or bilateral disease on chest X-ray. Categorical variables were modelled as dummy variables.

Next, we performed multivariable analyses, including all covariates evaluated in the univariable analysis, to estimate adjusted odds ratios (aOR). We first conducted multivariable analyses on the entire dataset. We then stratified the dataset on the use of Group A drugs (none; moxifloxacin/levofloxacin only; bedaquiline with or without moxifloxacin/levofloxacin; linezolid with or without moxifloxacin/levofloxacin; bedaquiline and linezolid with or without moxifloxacin/levofloxacin), and conducted multivariable analyses to assess the effect of drug resistance patterns on treatment outcomes in these five subgroups. For this latter analysis, due to the limited number HIV infected patients not receiving ART, we simplified the HIV covariate as HIV-positive vs. HIV-negative. We also conducted multivariable analyses stratified for the following drug resistance patterns: MDR "*sensu stricto*"; FQ-susceptible MDR (i.e. MDR "*sensu stricto*" and MDR+SLID resistance combined); MDR+FQ resistance; MDR+SLID resistance; and XDR-TB.

Finally, we repeated each multivariable analysis, excluding patients lost-to-follow-up or transferred out, as a sensitivity analysis.

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Ethics

This study was approved by an ethics committee of the Research Institute of the McGill University Health Center. Ethics approval was also obtained at participating sites, when necessary according to national or local regulations.

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication. The findings and conclusions are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

Results

Patient characteristics

Table 1 shows the characteristics of the included patients (N=11,666). They were mostly male (N=7137, 61.2%), aged 26-45 years (N=6671, 57.2%), from upper-middle income countries (N=6598, 56.6%), and HIV-negative (N=7715, 66.1%). Overall, 7446 (63.8%) had MDR-TB "*sensu stricto*", 2402 (20.6%) "pre-XDR-TB" (N=1319, 11.3% with SLID resistance; N=1083, 9.3% with FQ resistance), and 1818 (15.6%) XDR-TB. Actual treatment duration was available for 9312 (79.8%) patients, with a median (interquartile range) of 19.8 (13.9-24.0) months. Data were imputed for 69 (0.6%) patients for site of TB, 800 (6.9%) patients for HIV status, 1714 (14.7%) patients for treatment history, and 3370 (28.9%), 6310 (54.1%), 4388 (37.6%) and 6637 (56.9%) patients for drug susceptibility to ethambutol, pyrazinamide, ethionamide/prothionamide and PAS, respectively.

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Treatment outcomes

Treatment outcome was favourable in 7013 patients (60.1%). Cycloserine/terizidone was used in 9287 patients (79.6%), linezolid in 1935 patients (16.6%), bedaquiline in 1926 patients (16.5%), and clofazimine in 1490 patients (12.8%). Most (n=10,867, 93.2%) patients received a FQ (7500 [64.3%] either moxifloxacin or levofloxacin). Drug resistance to FQs (aOR 1.91; 95%CI 1.63-2.23), SLIDs (aOR 1.53, 95% CI 1.33-1.75) and FQs plus SLIDs (XDR-TB; aOR 2.03, 95% CI 1.74-2.37) increased the odds of an unfavourable treatment outcome compared to patients with MDR-TB "*sensu stricto*" (**Figure 1, Appendix E2**).

We obtained similar findings when restricting the analysis to persons who received neither linezolid nor bedaquiline, regardless of moxifloxacin/levofloxacin use. When linezolid, bedaquiline or both were prescribed, patients with all the specified drug resistance patterns (MDR-TB "*sensu stricto*", "pre-XDR-TB" and XDR-TB) had comparable treatment outcomes (**Table 2, Appendix E2**).

Effect of specific drugs on treatment outcomes

In the full analysis combining all evaluated resistance patterns, we found no association between unfavourable treatment outcomes and moxifloxacin/levofloxacin use in patients receiving neither bedaquiline nor linezolid. Linezolid and/or bedaquiline were associated with decreased odds of unfavourable outcome, particularly when combined (aOR 0.30, 95% CI 0.23-0.38; compared with 0.63, 95% CI 0.49-0.83 for linezolid only; and 0.47, 95% CI 0.36-0.59 for bedaquiline only; **Figure 1**). The inclusion of clofazimine and/or cycloserine/terizidone did not significantly affect the odds of unfavourable outcomes **(Figure 1).**

These benefits of linezolid and bedaquiline were confirmed when stratifying by drug resistance pattern (**Figure 2, Appendix E3**), particularly in patients with resistance to FQs (**Figure 2c**; **Figure 2e**). In patients whose strain was susceptible to FQs (**Figure 2b**), linezolid did not appear to significantly impact treatment outcomes (aOR 0.94, 95% CI 0.67–1.32), and the effect of bedaquiline was smaller

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(aOR 0.53, 95% CI 0.40–0.70 for bedaquiline only; aOR 0.39, 95% CI 0.29–0.54 for bedaquiline plus linezolid). Moxifloxacin/levofloxacin use had no significant impact on unfavourable outcome among patients with MDR "*sensu stricto*" or "pre-XDR" TB. Among XDR-TB patients, those receiving moxifloxacin/levofloxacin had higher odds of unfavourable outcome (aOR 1.54, 95% CI 1.01-2.36). The use of FQs other than moxifloxacin/levofloxacin in the reference group (no Group A drugs) was clearly lower among patients with XDR-TB than with other drug resistance patterns (**Appendix E4**).

Results from the sensitivity analysis excluding patients lost to follow-up were similar to the main analysis, except for patients treated with bedaquiline and without linezolid: those with XDR-TB had higher odds of unfavourable outcome compared with MDR-TB "*sensu stricto*" (aOR 2.20, CI 1.25-3.87; **Appendix E5**).

Our analysis showed that MDR-TB "*sensu stricto*" plus additional drug resistance to any FQ was associated with unfavourable outcomes. In this situation, the risk of unfavourable outcome was clearly demonstrated where neither linezolid nor bedaquiline were used. Adding bedaquiline or linezolid to the regimen decreased the odds of unfavourable outcome, including in patients with FQ resistance. Consequently, treatment options with a resistance pattern that includes Group A drugs are extremely limited.

Discussion

Using a large international dataset, we found that the administration of bedaquiline and/or linezolid improved treatment outcomes in patients with MDR-TB. With the exception of linezolid only, which was found to improve outcomes only when FQ resistance was present, the positive effect was observed irrespective of available DST results as per current definitions (MDR "sensu stricto", "pre-XDR," or XDR).

Our results are consistent with a large multinational prospective study (20). Patients with MDR-TB treated without bedaquiline and linezolid had the best treatment outcomes when there was no

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resistance against FQ and SLID (MDR "*sensu stricto*"); treatment outcomes were intermediate when either FQ or SLID resistance was present ("pre-XDR-TB") and worst when there was resistance to any FQ and a SLID (XDR-TB). However, contrary to what emerged from previous studies informed by an older version of the IPDMA, we did not observe differences in treatment outcome between persons with MDR-TB plus resistance to SLID and those with MDR-TB plus resistance to FQ (4). The likely explanation is the substantial difference between the two IPDMA cohorts. In the more recent one, a much higher proportion of patients had access to new and repurposed drugs, overcoming the lack of effective drugs in the previous cohort. This is confirmed by the higher success rates in the second cohort than the previous one in patients with the same drug resistance profile. Our results are however consistent with the latest WHO recommendations considering bedaquiline and linezolid, together with the FQs, as preferred drugs for patients with MDR-"*sensu stricto*", "pre-XDR-" or XDR-TB (8,9,21). Treatment outcomes were slightly better when bedaquiline and linezolid were combined than when only one of the two was used.

When FQ were used without bedaquiline or linezolid, the odds of unfavorable outcome increased over two-fold with the presence of FQ resistance and modestly (1.5-fold) with the presence of SLID resistance, likely due to additional resistances associated with SLID (4). A recent IPDMA study suggests that moxifloxacin/levofloxacin use is associated with significantly more favourable outcomes when compared to persons who did not receive any FQ. Conversely, in our analysis, the reference group still largely received older-generation FQs. This explains the unexpected finding that moxifloxacin/levofloxacin did not significantly improve outcomes, even when bacilli were susceptible to the FQs.

The new information from large-scale implementation projects in South Africa and other studies supports the WHO recommendation to use bedaquiline to treat MDR-TB (30). Furthermore, the recent demonstration in an open-label, single-arm trial of the efficacy of the new BPaL regimen (bedaquiline, pretomanid and linezolid for 6-9 months) followed by its FDA approval (21,31) underlines the

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importance of the bedaquiline-linezolid combination in a regimen that also includes the new nitroimidazole compound pretomanid. The trial data showed also a high frequency of adverse reactions (peripheral neuropathy, bone marrow suppression), largely attributable to linezolid at the dose of 1200 mg/day, twice as high as in the IPDMA and other studies (15,32). Given the trial results leading to the FDA approval and our data confirming the importance of the bedaquiline-linezolid combination, research towards lower doses (or shorter courses) of linezolid, or new, less toxic oxazolidinones, are top priority. A fully oral 6-month regimen that maintains the potency of BPaL while minimising the linezolid-related adverse events would be a major advance for effective care of any form of TB.

The 2006 definition of XDR-TB used until 2020 has become obsolete as SLID are now recommended by WHO to be used for the MDR-TB treatment only when there is no other option (8,9). Our results were presented in the WHO expert hearing in October 2020 and contributed to the discussion about the new categorization of drug resistance levels (33). Our findings support the revised definition of XDR-TB as “MDR/RR-TB with additional resistance to any fluoroquinolone and either bedaquiline or linezolid”, and the newly introduced definition of pre-XDR-TB as “MDR/RR-TB with additional bacterial resistance to any fluoroquinolone.” Of note, these new definitions reflect different levels of drug resistance. They do not consider other factors, e.g. severity of disease, strength of immune response, or endotype, that may influence treatment outcomes.

While other possibilities to re-define XDR-TB exist, a solid new definition adapted to the updated 2019 and 2020 MDR-TB treatment guidelines (8,9) is difficult due to the limited information available on DST for key drugs like bedaquiline and linezolid. Our results showed that the risk of unfavourable outcome was the lowest in patients who received both linezolid and bedaquiline. The findings could thus be compatible with a stricter definition of XDR-TB, or adding another level beyond XDR-TB with resistance to all Group A drugs. If resistance to those drugs is systematically monitored and well documented through operationally applicable technologies in the coming years, one will be able to

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compare treatment success rates according to such resistance, and elaborate new definitions that combine surveillance and treatment regimen guidance purposes.

Our study has several limitations. First, the most important limitation of this study is the utilization of use/exposure to different drugs in informing resistance-based definitions. This is mainly due to practical limitations in the data. The information on possible drug resistance for the new recommended drugs was often missing, with DST results available for only 36% of patients for cycloserine/terizidone, 7% for linezolid, 2% for clofazimine. No reliable information was available on bedaquiline resistance. Consequently, in some patients receiving those drugs the drug may not have been effective (particularly cycloserine/terizidone, and to a lesser extent, clofazimine). Drug susceptibility testing for many drugs including bedaquiline and linezolid also remains limited in practice, which restricts the application of XDR-TB definition based on the resistance to these drugs. However, new technologies such as rapid next generation sequencing are likely to improve provision of accurate medicines in combination treatment regimens and making universal access to DST for all WHO Group medicines easier (33). Other potentially relevant information, such as the duration of exposure, changes to the treatment regimen, and dosing of linezolid, was also missing. Second, the number of patients in the sensitivity analysis using complete cases only was too small to enable a meaningful analysis. Third, the selection of studies included in the IPDMA may be biased, as it relies on the will of investigators to share their data. The long time period and varied geographic settings could also bias the analyses. We attempted to mitigate this by adjusting for the country-level income and the year of treatment initiation, and by accounting for study-level clustering. Finally, the analysis excluded patients with confirmed susceptibility or unknown resistance status to isoniazid. The updated definitions of pre-XDR- and XDR-TB proposed by the WHO are based on MDR/RR-TB (34) and we acknowledge that the applicability of our results to patients with isoniazid susceptible RR-TB may be limited.

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All patients in our study received the previously recommended longer MDR-TB treatment regimen (35): the IPDMA data did not include patients treated with a standardized shorter MDR-TB regimen (36). The effectiveness and safety of that regimen were evaluated in a separate study (37), and a recent comparison based on the same IPDMA cohort of those two regimens confirmed that their effectiveness and safety were similar (14,38). Further analysis including any shorter regimen would be necessary to investigate the role beyond surveillance that new definitions of drug-resistant TB would have in operational terms to guide use of different regimens according to the drug resistance pattern (39).

In conclusion, our study confirmed the effectiveness of the combination of bedaquiline and linezolid in the treatment of all forms of pulmonary MDR-TB, adding information towards new definitions that are useful for clinical management of drug-resistant tuberculosis. Our results support the newly introduced WHO definition of "pre-XDR-TB" as MDR plus additional resistance to any FQ, and the updated definition of XDR-TB as MDR plus additional resistance to any FQ plus bedaquiline and/or linezolid (≥two out of three Group A drugs). In the coming years, systematically assessing the effectiveness of any recommended drugs and monitoring the possible emergence of resistance to them remains crucial. This will also help assess the adequacy of new definitions of MDR-TB "*sensu stricto*", "pre-XDR-TB" and XDR-TB for surveillance purposes as well as to define specific treatment options.

Acknowledgments

The article is part of the activities of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, ITA-80, 2017-2020- GBM/RC/LDA.).

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Figure legends

Figure 1: Estimates of the effect of drug resistance pattern and effective use of newly upgraded drugs on drug-resistant tuberculosis treatment outcome. Odds ratios of unfavourable outcomes from multivariable logistic regression with 95% confidence intervals are shown.

[Footnote]: Unfavourable outcome: treatment failure, relapse, death or loss to follow-up. MDRss = multidrug resistant tuberculosis "sensu stricto"; FQ = floroquinolones; SLID = second-line injectable drugs: Mfx, moxifloxacin; Lfx, levofloxacin; Bdq, bedaquiline; Lzd, linezolid. The results are adjusted for drug resistance group, use of moxifloxacin/levofloxacin, bedaquiline and linezolid, use of clofazimine and cycloserine/terizidone, use of carbapenems, number of effective drugs used apart from FQ, SLID, linezolid, bedaquiline, clofazimine, cycloserine/terizidone and carbapenems (0; 1; $\geqslant$ 2), prior TB treatment (none; first-line drugs only; any second-line drugs), age in years ($\leqslant$25; 26-45; >45), gender, HIV status (HIV-negative; HIV-positive without antiretroviral therapy (ART); HIV positive with ART), country classification by income level (lower-middle; upper-middle; high), year of treatment initiation (<2003, 2004-2008, 2009-2012, 2013-2016), and extended TB disease (presence of extensive tuberculosis disease based acid-fast bacilli (AFB) smear status, cavitation or bilateral disease on chest X-ray.

Figure 2: Estimates of the effect of exposure to WHO Group A drugs on drug-resistant tuberculosis treatment outcome, stratified by drug resistance pattern. Odds ratios of unfavourable outcomes from multivariable logistic regression are shown.

[Footnote]: Unfavourable outcome: treatment failure, relapse, death or loss to follow-up. MDR, multidrug-resistant tuberculosis; FQ, floroquinolones; SLID, second-line injectable drugs; XDR, extensively drug-resistant tuberculosis; Mfx, moxifloxacin; Lfx, levofloxacin; Bdq, bedaquilin; Lzd, linezolid. The results are adjusted for use of moxifloxacin/levofloxacin, bedaquiline and linezolid, use of clofazimine and cycloserine/terizidone, use of carbapenems, number of effective drugs used apart

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from FQ, SLID, linezolid, bedaquiline, clofazimine, cycloserine/terizidone and carbapenems (0; 1; ⩾ 2), prior TB treatment (none; first-line drugs only; any second-line drugs), age in years (⩽25; 26-45; >45), gender, HIV status (HIV-negative; HIV-positive without antiretroviral therapy (ART); HIV positive with ART), country classification by income level (lower-middle; upper-middle; high), year of treatment initiation (<2003, 2004-2008, 2009-2012, 2013-2016), and extended TB disease (presence of extensive tuberculosis disease based acid-fast bacilli (AFB) smear status, cavitation or bilateral disease on chest X-ray.

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Tables

Table 1: Characteristics of the included patients from the individual patient data meta-analysis database.

	All selected IPD patients (N = 11666)	Number (%) of patients with favourable outcome	Number (%) among with unfavourable outcome.
Outcome*			
Favourable	7013 (60.1%)	7013 (100.0%)	0 (0.0%)
Unfavourable	4653 (39.9%)	0	4653 (100.0%)
Drug resistance pattern			
MDRss	7446 (63.8%)	4740 (67.6%)	2706 (58.2%)
MDRss + FQ	1083 (9.3%)	654 (9.3%)	429 (9.2%)
MDRss + SLID	1319 (11.3%)	791 (11.3%)	528 (11.3%)
XDR	1818 (15.6%)	828 (11.8%)	990 (21.3%)
Use of Group A drugs			
None	3780 (32.4%)	1888 (26.9%)	1892 (40.7%)
Mfx/Lfx only	5215 (44.7%)	3255 (46.4%)	1960 (42.1%)
Linezolid with or without Mfx/Lfx	745 (6.4%)	543 (7.7%)	202 (4.3%)
Bedaquline with or without Mfx/Lfx	736 (6.3%)	469 (6.7%)	267 (5.7%)
Linezolid+ bedaquiline with or without Mfx/Lfx	1190 (10.2%)	858 (12.2%)	332 (7.1%)
Use of Group B drugs			
None	2067 (17.7%)	1090 (15.5%)	977 (21%)
Clofazimine only	312 (2.7%)	224 (3.2%)	88 (1.9%)
Cycloserine/terizidone only	8109 (69.5%)	4949 (70.6%)	3160 (67.9%)
Clofamizine + cycloserine/terizidone	1178 (10.1%)	750 (10.7%)	428 (9.2%)
Use of carbapenems			
No	11418 (97.9%)	6825 (97.3%)	4593 (98.7%)
Yes	248 (2.1%)	188 (2.7%)	60 (1.3%)
Number of effective drugs**			
0	6236 (53.5%)	3456 (49.3%)	2780 (59.7%)
1	3826 (32.8%)	2435 (34.7%)	1391 (29.9%)
≥ 2	1604 (13.7%)	1122 (16.0%)	482 (10.4%)
Past TB treatment			
FQ	4604 (39.5%)	2830 (40.4%)	1774 (38.1%)
SLID	2056 (17.6%)	1060 (15.1%)	996 (21.4%)
None	3292 (28.2%)	2198 (31.3%)	1094 (23.5%)
Unknown	1714 (14.7%)	925 (13.2%)	789 (17%)
HIV status			
Negative	7715 (66.1%)	5037 (71.8%)	2678 (57.6%)
HIV, no ART	672 (5.8%)	247 (3.5%)	425 (9.1%)
HIV with ART	2479 (21.2%)	1383 (19.7%)	1096 (23.6%)
Unknown	800 (6.9%)	346 (4.9%)	454 (9.7%)
Sex			
Male	7137 (61.2%)	4190 (59.7%)	2947 (63.3%)
Female	4529 (38.8%)	2823 (40.3%)	1706 (36.7%)
Age (years)			
≤ 25	2135 (18.3%)	1320 (18.8%)	815 (17.5%)
26 - 45	6671 (57.2%)	3939 (56.2%)	2732 (58.7%)
> 45	2860 (24.5%)	1754 (25.0%)	1106 (23.8%)
Country income			
Lower-middle	1525 (13.1%)	930 (13.3%)	595 (12.8%)
Upper-middle	6598 (56.6%)	3496 (49.9%)	3102 (66.7%)
High	2592 (22.2%)	1925 (27.4%)	667 (14.3%)
Unknown	951 (8.1%)	662 (9.4%)	289 (6.2%)

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Year of treatment start			
≤ 2003	1661 (14.2%)	847 (12.1%)	814 (17.5%)
2004-2008	4146 (35.5%)	2321 (33.1%)	1825 (39.2 %)
2009-2012	2056 (17.6%)	1431 (20.4%)	625 (13.4%)
2013-2016	3803 (32.6%)	2414 (34.4%)	1389 (29.9%)
Extended TB disease			
No	2881 (24.7%)	1947 (27.8%)	934 (20.1%)
Yes	6873 (58.9%)	4090 (58.3%)	2783 (59.8%)
Unknown	1912 (16.4%)	976 (13.9%)	936 (20.1%)

** Treatment outcome was defined as unfavourable if the treatment failed, if a relapse occurred, or if the patient died or was lost-to-follow-up. Treatment outcome was defined to be favourable in case of cure, or if the treatment was completed with no reported failure or relapse.*

*** The number of effective drugs here is the number of effective drugs used apart from fluoroquinolones (FQ), second-line injectable drugs (SLID), linezolid, bedaquiline, clofazimine, cycloserine (Cs)/terizidone (Trd) and carbapenems.*

IPD = individual patient data; MDR = multidrug resistant; ss = "sensu-stricto" (neither FQ nor SLID resistance); XDR = extensively drug resistant; TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral therapy; Mfx, moxifloxacin; Lfx, levofloxacin.

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Table 2: Estimates of the effect of drug resistance pattern on treatment outcomes of drug-resistant tuberculosis from multivariable logistic regression, stratified per Group A drug (moxifloxacin[Mfx]/levofloxacin[Lfx], linezolid, bedaquiline) use. The effect size is reported as adjusted odds ratio of unfavourable treatment outcome.

	No use of linezolid, bedaquiline, or Mfx/Lfx (N = 3780)	Used Mfx/Lfx, no use of bedaquiline or linezolid (N = 5215)	Used linezolid without bedaquiline (with or without Mfx/Lfx) (N = 745)	Used bedaquiline without linezolid (with or without Mfx/Lfx) (N = 736)	Used linezolid + bedaquiline (with or without Mfx/Lfx) (N = 1190)
Drug resistance pattern (0 missing before imputation)	P < 0.001	P < 0.001	P = 0.42	P = 0.23	P = 0.26
MDRss	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
MDRss + FQ	1.50 (0.99 – 2.26)	2.20 (1.74 – 2.77)	0.97 (0.55 - 1.71)	1.04 (0.64 - 1.69)	1.16 (0.76 - 1.78)
MDRss + SLID	1.80 (1.40 – 2.32)	1.49 (1.21 – 1.84)	0.66 (0.37 - 1.17)	1.38 (0.82 - 2.31)	0.75 (0.48 - 1.18)
XDR	4.04 (2.75 – 5.94)	2.96 (2.24 – 3.91)	0.76 (0.44 - 1.32)	1.57 (0.98 - 2.53)	0.89 (0.62 - 1.28)

FQ = fluoroquinolones; SLID = second-line injectable drugs; Lzd = linezolid; Bdq = bedaquiline; MDR = multidrug resistant; ss = "sensu-stricto" (neither FQ nor SLID resistance); XDR = extensively drug resistant

Unfavourable outcome: treatment failure, relapse, death or loss to follow-up. The analysis is adjusted for drug resistance group, use of clofazimine and cycloserine/terizidone, use of carbapenems, number of effective drugs used apart from FQ, SLID, linezolid, bedaquiline, clofazimine, cycloserine/terizidone and carbapenems (0; 1; ⩾2), prior TB treatment (none; first-line drugs only; any second-line drugs), age in years (⩽25; 26-45; >45), gender, HIV status (HIV-negative; HIV-positive without antiretroviral therapy (ART); HIV positive with ART), country classification by income level (lower-middle; upper-middle; high), year of treatment initiation (<2003, 2004-2008, 2009-2012, 2013-2016), and extended TB disease (presence of extensive tuberculosis disease based acid-fast bacilli (AFB) smear status, cavitation or bilateral disease on chest X-ray.

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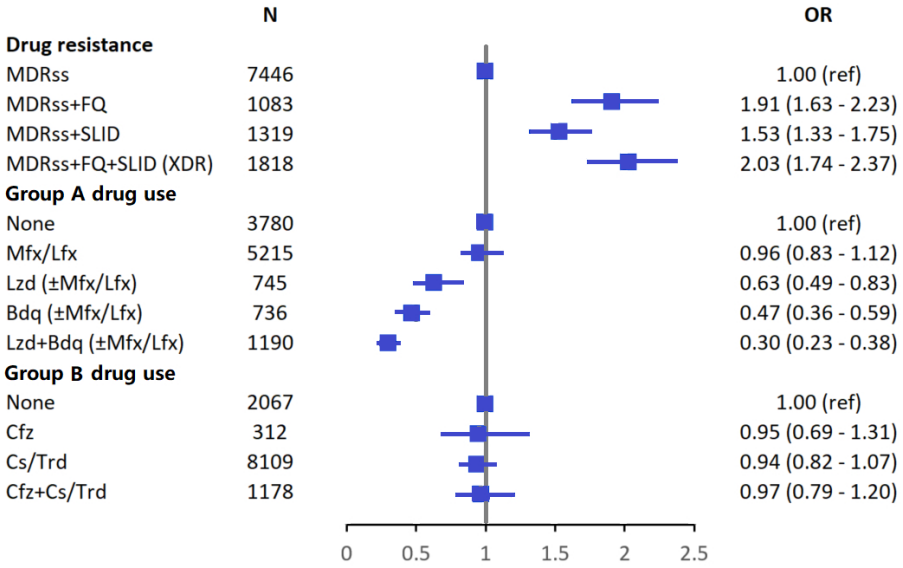

Figure 1: Estimates of the effect of drug resistance pattern and effective use of newly upgraded drugs on drug-resistant tuberculosis treatment outcome. Odds ratios of unfavourable outcomes from multivariable logistic regression with 95% confidence intervals are shown.

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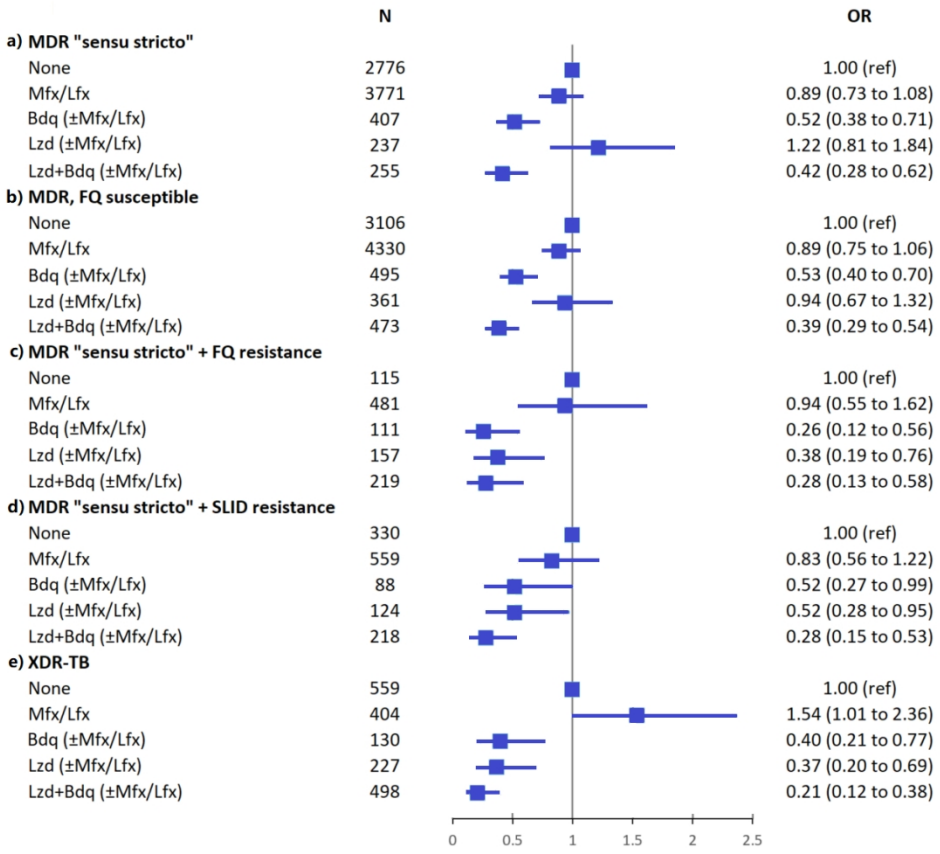

Figure 2: Estimates of the effect of exposure to WHO Group A drugs on drug-resistant tuberculosis treatment outcome, stratified by drug resistance pattern. Odds ratios of unfavourable outcomes from multivariable logistic regression are shown.

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Evidence-based Definition for Extensively Drug-resistant Tuberculosis

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Online Data Supplement

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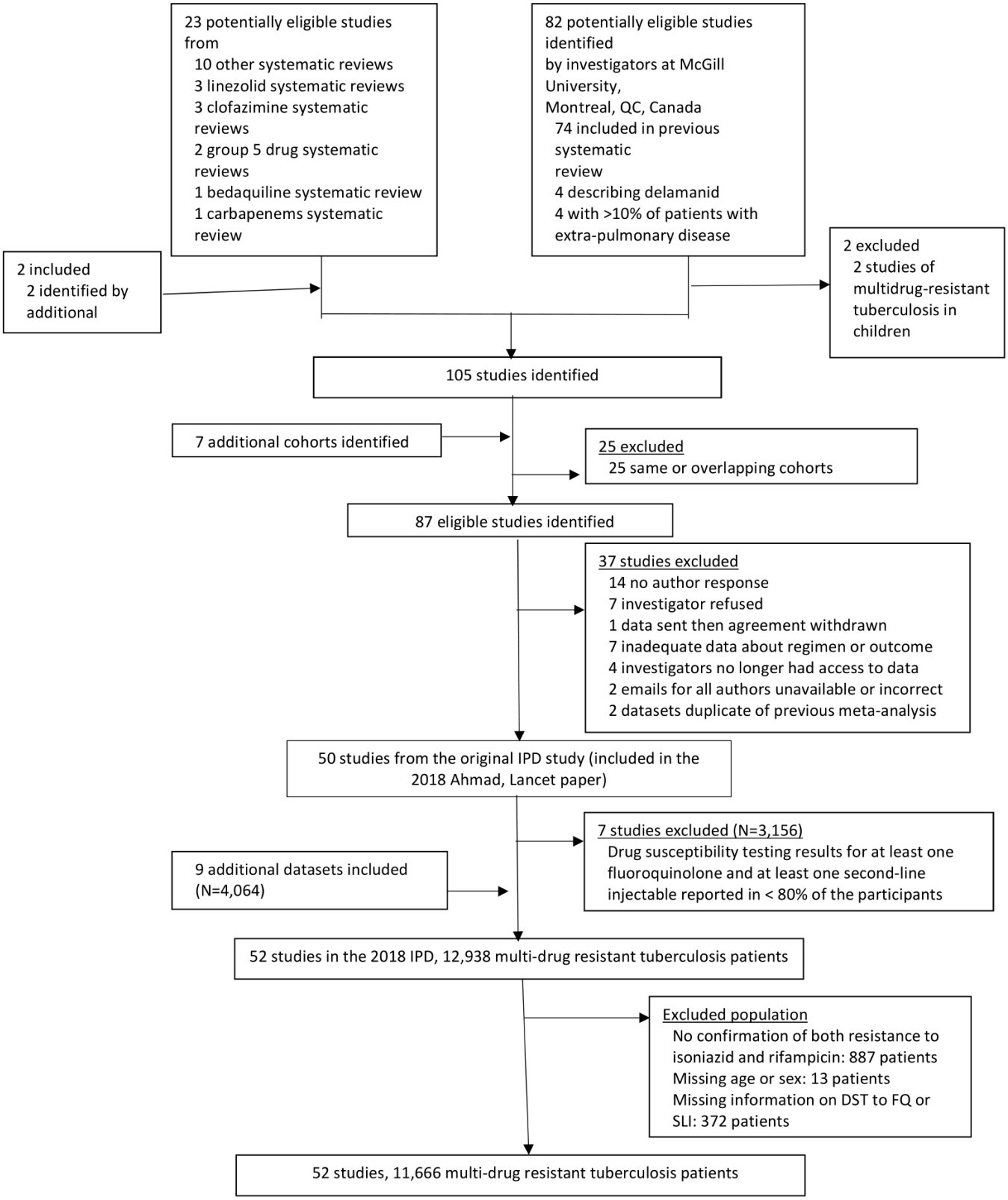
Appendix E1: Flow diagram for studies included in the individual patient data meta-analysis, adapted from Bisson et al. 2020 (E1).



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Appendix E2: Association of covariates with treatment outcome, from logistic regression models, for the main analysis. From left to right and from top to bottom: univariable analysis on the whole data set, multivariable analysis on the whole data set, multivariable analysis for subgroups depending on the use of linezolid and/or bedaquiline. An "X" means that the level of the covariate was not represented in the subgroup of interest, or that confidence interval reached infinity because of the small number of patients. The results are presented as (unadjusted or adjusted) odds ratios for an unfavourable outcome.

	N=11666	All – Univariable	All – Multivariable	No Mfx/Lfx, linezolid or bedaquiline - Multivariable (N=3780)	Mfx/Lfx – Multivariable (N=5215)	Linezolid (±Mfx/Lfx) – Multivariable (N=745)	Bedaquiline (±Mfx/Lfx) – Multivariable (N=736)	Bedaquiline + Linezolid (±Mfx/Lfx) – Multivariable (N=1190)
Drug resistance (0 missing before imputation)		P<0.001	P<0.001	P<0.001	P<0.001	P=0.44	P=0.22	P=0.26
MDRss	7446	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
MDRss+FQ	1083	1.15 (1.01-1.31)	1.91 (1.63-2.23)	1.49 (0.99-2.25)	2.20 (1.74-2.76)	0.98 (0.56-1.73)	1.07 (0.66-1.74)	1.16 (0.76-1.77)
MDRss+SLID	1319	1.17 (1.04-1.32)	1.53 (1.33-1.75)	1.78 (1.38-2.30)	1.49 (1.21-1.85)	0.67 (0.37-1.18)	1.35 (0.81-2.27)	0.75 (0.48-1.18)
XDR	1818	2.09 (1.89-2.32)	2.03 (1.74-2.37)	3.91 (2.69-5.68)	2.96 (2.24-3.92)	0.78 (0.45-1.34)	1.60 (0.99-2.58)	0.89 (0.62-1.28)
Number of effective drugs (except FQ, SLID, linezolid, bedaquiline, clofazimine, Cs/Trd, Ipm/Mpm) (0 missing before imputation)		P<0.001	P<0.001	P=0.002	P=0.36	P=0.83	P=0.14	P=0.96
0	6361	1.37 (1.26-1.48)	1.24 (1.10-1.40)	1.35 (1.13-1.61)	1.16 (0.94-1.42)	0.95 (0.63-1.42)	1.64 (0.92-2.93)	0.96 (0.57-1.63)
1	3799	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≥2	1506	0.75 (0.66-0.85)	1.00 (0.86-1.16)	0.97 (0.75-1.27)	1.00 (0.81-1.23)	0.81 (0.41-1.60)	1.87 (0.92-2.93)	0.87 (0.32-2-37)
Cfz, Cs/Trd use (0 missing before imputation)		P<0.001	P=0.76	P=0.05	P=0.02	P=0.74	P=0.58	P=0.73
None	2067	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Cfz	312	0.44 (0.34-0.57)	0.95 (0.69-1.31)	0.63 (0.14-2.81)	0.76 (0.38-1.53)	1.22 (0.63-2.35)	0.43 (0.12-1.52)	1.10 (0.51-2.36)
Cs/Trd	8109	0.71 (0.65-0.79)	0.94 (0.82-1.07)	0.93 (0.78-1.11)	0.70 (0.53-0.91)	1.31 (0.81-2.12)	0.99 (0.58-1.70)	0.94 (0.51-1.73)
Cfz + Cs/Trd	1178	0.64 (0.55-0.74)	0.97 (0.79-1.20)	0.17 (0.05-0.61)	0.90 (0.61-1.34)	1.15 (0.58-2.26)	1.03 (0.49-2.15)	0.84 (0.44-1.60)
Ipm/Mpm use (0 missing before imputation)		P<0.001	P=0.56	P=1.00	P=0.60	P=0.19	P=0.09	P=0.98
No	11418	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	248	0.47 (0.35-0.64)	1.13 (0.74-1.73)	X	0.71 (0.20-2.53)	1.65 (0.79-3.46)	5.83 (0.75-45.11)	1.01 (0.45-2.27)
Past TB treatment (1714 missing before imputation)		P<0.001	P<0.001	P=0.004	P<0.001	P=0.44	P=0.002	P=0.27
FLD	4604	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
SLD	2056	1.50 (1.35-1.66)	1.41 (1.21-1.63)	1.56 (1.13-2.16)	1.39 (1.13-1.72)	1.37 (0.77-2.41)	1.68 (1.05-2.69)	0.89 (0.63-1.27)
None	3292	0.79 (0.72-0.87)	0.83 (0.75-0.93)	0.98 (0.80-1.21)	0.73 (0.62-0.85)	1.34 (0.79-2.27)	0.66 (0.43-1.01)	1.21 (0.84-1.73)

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(Appendix E2, continuation)

	N=11666	All – Univariable	All – Multivariable	No Mfx/Lfx, linezolid or bedaquiline - Multivariable (N=3780)	Mfx/Lfx – Multivariable (N=5215)	Linezolid (±Mfx/Lfx) – Multivariable (N=745)	Bedaquiline (±Mfx/Lfx) – Multivariable (N=736)	Bedaquiline + Linezolid (±Mfx/Lfx) – Multivariable (N=1190)
Sex (0 missing before imputation)		P<0.001	P<0.001	P<0.001	P<0.001	P=0.35	P=0.77	P=0.32
Male	7137	1.16 (1.08-1.26)	1.25 (1.15-1.37)	1.38 (1.18-1.63)	1.26 (1.11-1.44)	1.19 (0.82-1.73)	0.95 (0.69-1.33)	1.15 (0.87-1.52)
Female	4529	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Age (yrs) (0 missing before imputation)		P=0.023	P=0.82	P=0.05	P=0.08	P=0.05	P=0.83	P=0.63
≤25	2135	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
26-45	6671	1.12 (1.02-1.24)	1.00 (0.89-1.12)	0.91 (0.75-1.11)	1.06 (0.89-1.26)	0.93 (0.59-1.47)	0.96 (0.62-1.50)	1.16 (0.79-1.69)
>45	2860	1.02 (0.91-1.15)	1.03 (0.91-1.17)	0.77 (0.61-0.96)	1.22 (1.00-1.49)	1.63 (0.94-2.81)	0.87 (0.52-1.44)	1.01 (0.65-1.58)
HIV status (800 missing before imputation)*		P<0.001	P<0.001	P=0.005	P<0.001	P=0.48	P=0.09	P=0.94
Negative	7715	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Positive	N/A	N/A	N/A	1.69 (1.19-2.39)	1.67 (1.39-2.01)	1.25 (0.68-2.31)	1.45 (0.94-2.24)	0.99 (0.71-1.37)
Positive no ART	672	3.24 (2.75-3.81)	1.88 (1.32-2.68)	N/A	N/A	N/A	N/A	N/A
Positive with ART	2479	1.49 (1.36-1.63)	1.39 (1.22-1.59)	N/A	N/A	N/A	N/A	N/A
Country income (951 missing before imputation)		P<0.001	P<0.001	P=0.27	P<0.001	P<0.001	P=0.39	P=0.02
Low-middle	1525	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Upper-middle	6598	1.39 (1.24-1.55)	1.16 (0.76-1.78)	1.02 (0.51-2.04)	1.14 (0.65-1.98)	3.18 (1.08-9.40)	2.23 (0.21-23.31)	0.81 (0.25-2.64)
High	2592	0.54 (0.47-0.62)	0.71 (0.47-1.10)	0.79 (0.38-1.66)	0.50 (0.30-0.85)	0.68 (0.26-1.81)	0.96 (0.07-13.65)	0.23 (0.06-0.93)
Year of treatment start (0 missing before imputation)		P<0.001	P=0.01	P=0.61	P=0.01	P=0.12	P=0.61	P=0.43
≤2003	1661	1.67 (1.49-1.88)	1.54 (1.04-2.28)	1.23 (0.42-3.62)	1.15 (0.64-2.09)	2.14 (0.56-8.26)	X	X
2004-2008	4146	1.37 (1.25-1.50)	1.61 (1.18-2.21)	0.99 (0.35-2.81)	1.81 (1.15-2.84)	1.72 (0.87-3.38)	1.50 (0.39-5.76)	X
2009-2012	2056	0.76 (0.68-0.85)	1.16 (0.88-1.51)	1.16 (0.40-3.40)	1.21 (0.82-1.78)	0.90 (0.51-1.59)	1.64 (0.61-4.42)	1.35 (0.64-2.86)
2013-2016	3803	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Extended disease (1912 missing before imputation)		P<0.001	P<0.001	P=0.007	P<0.001	P=0.05	P=0.39	P=0.06
No	2881	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	6873	1.42 (1.29-1.55)	1.42 (1.27-1.58)	1.39 (1.10-1.76)	1.52 (1.31-1.76)	1.60 (1.00-2.56)	1.22 (0.78-1.92)	1.40 (0.98-1.99)

ss = "sensu-stricto" (neither FQ nor SLID resistance); FQ = fluoroquinolones; SLID = second-line injectable drugs; Mfx=moxifloxacin; Lfx, levofloxacin; Cfz = clofazimine; Cs = cycloserine; Trd = terizidone; Ipm = imipenem; Mpm = meropenem; MDR = multidrug resistant; XDR = extensively drug resistant; TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral therapy

Unfavourable outcome: treatment failure, relapse, death or loss to follow-up. The results of multivariable analyses are adjusted for all variables (full analysis also for the use of Mfx/Lfx, bedaquilin and linezolid).

**In stratified analyses, all HIV positive patients were grouped together regardless of ART use*

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Appendix E3: Estimates of the effective use of newly upgraded drugs on treatment outcomes in patients with drug-resistant tuberculosis, for a) patients with MDR-TB "sensu stricto" without additional resistance to fluoroquinolones or second-line injectable drugs; b) patients with MDR-TB whose strain was proven susceptible to fluoroquinolones (i.e. categories a) and d) combined); c) patients with MDR-TB whose strain was proven resistant to fluoroquinolones; d) patients with MDR-TB whose strain was proven resistant to second-line injectable drugs; e) patients with XDR-TB. Adjusted odds ratios of unfavourable outcomes from logistic regressions are shown. The results are presented as adjusted odds ratios of an unfavourable treatment outcome.

a) MDR "*sensu stricto*" – Multivariable (N=7446)		
Group A drug use (0 missing before imputation)		P<0.001
	None	1.00 (ref)
	Mfx/Lfx	0.89 (0.73-1.08)
	Lzd (± Mfx/Lfx)	1.22 (0.81-1.84)
	Bdq (± Mfx/Lfx)	0.52 (0.38-0.71)
	Bdq + Lzd (± Mfx/Lfx)	0.42 (0.28-0.62)
Group B drug use (0 missing before imputation)		P=0.28
	None	1.00 (ref)
	Cfz	1.00 (0.58-1.73)
	Cs/Trd	0.92 (0.78-1.09)
	Cfz + Cs/Trd	1.25 (0.87-1.79)
b) FQ susceptible – Multivariable (N=8765)		
Group A drug use (0 missing before imputation)		P<0.001
	None	1.00 (ref)
	Mfx/Lfx	0.89 (0.75-1.06)
	Lzd (± Mfx/Lfx)	0.94 (0.67-1.32)
	Bdq (± Mfx/Lfx)	0.53 (0.40-0.70)
	Bdq + Lzd (± Mfx/Lfx)	0.39 (0.29-0.54)
Group B drug use (0 missing before imputation)		P=0.30
	None	1.00 (ref)
	Cfz	0.89 (0.56-1.40)
	Cs/Trd	0.93 (0.80-1.08)
	Cfz + Cs/Trd	1.13 (0.86-1.49)
c) MDR "*sensu stricto*" + FQ resistance – Multivariable (N=1083)		
Group A drug use (0 missing before imputation)		P<0.001
	None	1.00 (ref)
	Mfx/Lfx	0.94 (0.55-1.62)
	Lzd (± Mfx/Lfx)	0.38 (0.19-0.76)
	Bdq (± Mfx/Lfx)	0.26 (0.12-0.56)
	Bdq + Lzd (± Mfx/Lfx)	0.28 (0.13-0.58)
Group B drug use (0 missing before imputation)		P=0.64
	None	1.00 (ref)
	Cfz	0.65 (0.28-1.49)
	Cs/Trd	0.77 (0.47-1.26)
	Cfz + Cs/Trd	0.70 (0.38-1.30)

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(Appendix E3, continuation)

d) MDR "*sensu stricto*" + SLID resistance – Multivariable (N=1319)		
Group A drug use (0 missing before imputation)		P=0.001
	None	1.00 (ref)
	Mfx/Lfx	0.83 (0.56-1.22)
	Lzd (± Mfx/Lfx)	0.52 (0.28-0.95)
	Bdq (± Mfx/Lfx)	0.52 (0.27-0.99)
	Bdq + Lzd (± Mfx/Lfx)	0.28 (0.15-0.53)
Group B drug use (0 missing before imputation)		P=0.17
	None	1.00 (ref)
	Cfz	0.46 (0.19-1.09)
	Cs/Trd	0.76 (0.51-1.14)
	Cfz + Cs/Trd	0.57 (0.33-0.99)
e) XDR – Multivariable (N=1818)		
Group A drug use (0 missing before imputation)		P<0.001
	None	1.00 (ref)
	Mfx/Lfx	1.54 (1.01-2.36)
	Lzd (± Mfx/Lfx)	0.37 (0.20-0.69)
	Bdq (± Mfx/Lfx)	0.40 (0.21-0.77)
	Bdq + Lzd (± Mfx/Lfx)	0.21 (0.12-0.38)
Group B drug use (0 missing before imputation)		P=0.60
	None	1.00 (ref)
	Cfz	1.20 (0.66-2.20)
	Cs/Trd	1.20 (0.83-1.73)
	Cfz + Cs/Trd	1.01 (0.64-1.61)

ss = "sensu-stricto" (neither FQ nor SLID resistance); FQ = fluoroquinolones; SLID = second-line injectable drugs; Mfx = Moxifloxacin; Lfx = Levofloxacin; Lzd = linezolid; Bdq = bedaquiline; Cfz = clofazimine; Cs = cycloserine; Trd = terizidone; MDR = multidrug-resistant; XDR = extensively drug-resistant

Unfavourable outcome: treatment failure, relapse, death or loss to follow-up. The results are adjusted for use of moxifloxacin/levofloxacin, bedaquiline and linezolid, use of clofazimine and cycloserine/terizidone, use of carbapenems, number of effective drugs used apart from FQ, SLID, linezolid, bedaquiline, clofazimine, cycloserine/terizidone and carbapenems (0; 1; ⩾ 2), prior TB treatment (none; first-line drugs only; any second-line drugs), age in years (⩽25; 26-45; >45), gender, HIV status (HIV-negative; HIV-positive without antiretroviral therapy (ART); HIV positive with ART), country classification by income level (lower-middle; upper-middle; high), year of treatment initiation (<2003, 2004-2008, 2009-2012, 2013-2016), and extended TB disease (presence of extensive tuberculosis disease based acid-fast bacilli (AFB) smear status, cavitation or bilateral disease on chest X-ray.

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Appendix E4: Use of floroquinolones other than moxifloxacin or levofloxacin (i.e. ofloxacin, ciprofloxacin and gatifloxacin) in patients receiving no Group A drug (n=3780) stratified by drug resistance pattern.

Drug resistance pattern	Total number of patients	Number (%) of patients who received FQs
MDR "*sensu stricto*"	2776	2688 (96.8%)
MDR "*sensu stricto"* + FQ resistance	115	66 (57.4%)
MDR "*sensu stricto*" + SLID resistance	330	321 (97.3%)
XDR	559	134 (24.0%)

MDR, multidrug-resistant; XDR, extensively drug-resistance; FQ, floroquinolones; SLID, second-line injectable drugs

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Appendix E5: Association of covariates with treatment outcome, from logistic regression models, for the sensitivity analysis excluding patients who were lost to follow-up. From left to right and from top to bottom: univariable analysis on the whole data set, multivariable analysis on the whole data set, multivariable analysis for subgroups depending on the use of linezolid and/or bedaquiline. An "X" means that the level of the covariate was not represented in the subgroup of interest, or that confidence interval reached infinity because of the small number of patients. The results are presented as (unadjusted or adjusted) odds ratios for an unfavourable outcome.

	N=9784	All – Univariable	All – Multivariable	No Mfx/Lfx, linezolid or bedaquiline - Multivariable (N=3069)	Mfx/Lfx – Multivariable (N=4370)	Linezolid (±Mfx/Lfx) – Multivariable (N=659)	Bedaquiline (±Mfx/Lfx) – Multivariable (N=607)	Bedaquiline + Linezolid (±Mfx/Lfx) – Multivariable (N=1079)
Drug resistance (0 missing before imputation)		P<0.001	P<0.001	P<0.001	P<0.001	P=0.09	P=0.03	P=0.29
MDRss	6148	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
MDRss+FQ	929	1.42 (1.21-1.65)	2.34 (1.94-2.81)	2.12 (1.32-3.38)	2.40 (1.83-2.15)	1.60 (0.78-3.31)	0.94 (0.50-1.77)	1.15 (0.70-1.91)
MDRss+SLID	1079	1.23 (1.06-1.42)	1.70 (1.43-2.02)	2.41 (1.78-3.26)	1.46 (1.12-1.91)	0.58 (0.26-1.30)	1.21 (0.63-2.33)	0.67 (0.39-1.17)
XDR	1628	3.25 (2.90-3.65)	2.88 (2.40-3.46)	6.26 (4.30-9.17)	3.83 (2.80-5.23)	1.46 (0.71-2.97)	2.20 (1.25-3.87)	1.03 (0.67-1.58)
Number of effective drugs (except FQ, SLID, linezolid, bedaquiline, Cfz, Cs/Trd, Ipm/Mpm) (0 missing before imputation)		P<0.001	P<0.001	P<0.001	P=0.003	P=0.81	P=0.03	P=0.75
0	5394	1.75 (1.58-1.94)	1.50 (1.30-1.73)	1.75 (1.41-2.16)	1.44 (1.11-1.87)	0.87 (0.51-1.47)	2.15 (1.01-4.57)	1.10 (0.60-1.99)
1	3119	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≥2	1271	0.70 (0.59-0.83)	0.90 (0.74-0.98)	0.85 (0.59-1.22)	0.85 (0.65-1.11)	0.77 (0.30-1.97)	3.34 (1.29-8.66)	1.50 (0.53-4.22)
Cfz, Cs/Trd use (0 missing before imputation)		P<0.001	P=0.21	P=0.02	P=0.004	P=0.56	P=0.35	P=0.14
None	1715	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Cfz	284	0.47 (0.35-0.63)	1.11 (0.76-1.62)	0.28 (0.05-1.65)	0.71 (0.31-1.58)	1.36 (0.57-3.27)	0.52 (0.12-2.25)	2.28 (0.90-5.73)
Cs/Trd	6747	0.63 (0.57-0.71)	0.92 (0.78-1.08)	0.83 (0.67-1.03)	0.64 (0.45-0.90)	1.08 (0.57-2.06)	1.17 (0.56-2.41)	1.46 (0.66-3.21)
Cfz + Cs/Trd	1038	0.67 (0.57-0.79)	1.13 (0.88-1.45)	0.16 (0.04-0.62)	1.05 (0.65-1.70)	1.79 (0.76-4.19)	1.61 (0.70-3.69)	1.24 (0.54-2.83)
Ipm/Mpm use (0 missing before imputation)		P<0.001	P=0.02	P=1.00	P=0.51	P=0.22	P=0.04	P=0.88
No	9553	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	231	0.57 (0.41-0.80)	1.91 (1.13-3.26)	X	1.66 (0.36-7.58)	1.97 (0.67-5.85)	7.96 (1.14-55.74)	1.07 (0.43-2.70)
Past TB treatment (1434 missing before imputation)		P<0.001	P<0.001	P=0.003	P<0.001	P=0.80	P=0.07	P=0.22
FLD	3826	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
SLD	1745	1.84 (1.63-2.07)	1.48 (1.25-1.77)	1.65 (1.16-2.37)	1.53 (1.19-1.96)	1.16 (0.56-2.40)	1.26 (0.74-2.14)	1.38 (0.91-2.11)
None	2779	0.75 (0.67-0.84)	0.86 (0.74-0.98)	0.96 (0.75-1.24)	0.80 (0.66-0.97)	0.91 (0.45-1.85)	0.60 (0.35-1.06)	1.00 (0.66-1.52)

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(Appendix 5, continuation)

	N=9784	All – Univariable	All – Multivariable	No Mfx/Lfx, linezolid or bedaquiline - Multivariable (N=3069)	Mfx/Lfx – Multivariable (N=4370)	Linezolid (±Mfx/Lfx) – Multivariable (N=659)	Bedaquiline (±Mfx/Lfx) – Multivariable (N=607)	Bedaquiline + Linezolid (±Mfx/Lfx) – Multivariable (N=1079)
Sex (0 missing before imputation)		P=0.99	P=0.04	P=0.06	P=0.18	P=0.38	P=0.50	P=0.78
Male	5846	1.00 (ref)	1.12 (1.01-1.24)	1.21 (0.99-1.47)	1.12 (0.95-1.31)	1.24 (0.77-2.01)	0.87 (0.57-1.31)	1.05 (0.76-1.45)
Female	3938	1.00 (0.91-1.09)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00(ref)	1.00 (ref)	1.00 (ref)
Age (yrs) (0 missing before imputation)		P=0.002	P<0.001	P=0.87	P<0.001	P=0.003	P=0.24	P=0.51
≤25	1758	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
26-45	5572	1.25 (1.11-1.41)	1.13 (0.98-1.30)	0.94 (0.75-1.20)	1.28 (1.02-1.61)	0.96 (0.52-1.77)	1.52 (0.82-2.82)	1.28 (0.81-2.03)
>45	2454	1.20 (1.05-1.38)	1.37 (1.17-1.61)	0.94 (0.72-1.23)	1.74 (1.35-2.24)	2.53 (1.24-5.15)	1.77 (0.91-3.45)	1.33 (0.79-2.24)
HIV status (644 missing before imputation)*		P<0.001	P<0.001	P<0.001	P<0.001	P=0.38	P=0.10	P=0.59
Negative	6495	1.00 (ref)	1.00 (ref)	1.00(ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Positive		N/A	N/A	2.02 (1.37-2.97)	2.42 (1.91-3.06)	1.41 (0.65-3.07)	1.52 (0.92-2.52)	0.90 (0.62-1.32)
Positive no ART	541	4.11 (3.44-4.92)	2.15 (1.47-3.14)	N/A	N/A	N/A	N/A	N/A
Positive with ART	2104	1.80 (1.62-2.00)	1.70 (1.44-2.01)	N/A	N/A	N/A	N/A	N/A
Country income (790 missing before imputation)		P<0.001	P<0.001	P=0.07	P<0.001	P=0.004	P=0.70	P=0.007
Low-middle	1277	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Upper-middle	5468	1.51 (1.32-1.73)	1.14 (0.69-1.87)	0.99 (0.57-1.75)	1.12 (1.02-1.61)	5.91 (1.16-30.11)	0.92 (0.09-9.30)	0.57 (0.17-1.94)
High	2249	0.45 (0.38-0.53)	0.54 (0.33-0.88)	0.67 (0.37-1.20)	0.37 (0.20-0.67)	1.18 (0.27-5.22)	0.49 (0.03-7.23)	0.14 (0.03-0.58)
Year of treatment start (0 missing before imputation)		P<0.001	P<0.001	P=0.16	P=0.06	P=0.02	P=0.34	P=0.24
≤2003	1350	1.82 (1.59-2.09)	2.68 (1.63-4.41)	2.06 (0.70-6.06)	2.15 (0.98-4.73)	6.71 (1.19-37.77)	X	X
2004-2008	3408	1.44 (1.29-1.60)	2.14 (1.44-3.19)	1.46 (0.49-4.33)	2.24 (1.25-4.03)	3.09 (1.18-8.09)	1.09 (0.21-5.76)	X
2009-2012	1825	0.84 (0.74-0.97)	1.47 (1.04-2.06)	2.04 (0.65-6.38)	1.80 (1.07-3.04)	1.02 (0.48-2.17)	1.65 (0.83-3.27)	1.65 (0.71-3.81)
2013-2016	3201	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Extended disease (1594 missing before imputation)		P<0.001	P<0.001	P=0.004	P<0.001	P=0.002	P=0.81	P=0.07
No	2473	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	5717	1.47 (1.32-1.65)	1.60 (1.38-1.86)	1.69 (1.19-2.41)	1.68 (1.40-2.03)	3.03 (1.50-6.10)	1.07 (0.63-1.82)	1.47 (0.97-2.23)

ss = "sensu-stricto" (neither FQ nor SLID resistance); FQ = fluoroquinolones; SLID = second-line injectable drugs; Mfx=moxifloxacin; Lfx, levofloxacin; Cfz = clofazimine; Cs = cycloserine; Trd = terizidone; Ipm = imipenem; Mpm = meropenem; MDR = multidrug resistant; XDR = extensively drug resistant; TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral therapy

Unfavourable outcome: treatment failure, relapse, death or loss to follow-up. The results of multivariable analyses are adjusted for all variables (full analysis also for the use of Mfx/Lfx, bedaquilin and linezolid).

**In stratified analyses, all HIV positive patients were grouped together regardless of ART use*

AJRCCM Articles in Press. Published June 09, 2021 as 10.1164/rccm.202009-3527OC

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AJRCCM Articles in Press. Published June 09, 2021 as 10.1164/rccm.202009-3527OC