# Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes

Dennis Falzon[1], Neel Gandhi[2], Giovanni B. Migliori[3], Giovanni Sotgiu[4], Helen S. Cox[5], Timothy H. Holtz[6], Maria-Graciela Hollm-Delgado[7], Salmaan Keshavjee[8], Kathryn DeRiemer[9], Rosella Centis[3], Lia D'Ambrosio[3], Christoph G. Lange[10], Melissa Bauer[7,11] and Dick Menzies[7] on behalf of the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB[12]

**Affiliations:** [1]Stop TB Dept, World Health Organization, Geneva, Switzerland. [2]Divisions of General Internal Medicine, Infectious Diseases and Epidemiology, Albert Einstein College of Medicine, New York, NY, [8]Dept of Global Health and Social Medicine, Harvard Medical School, Boston, MA, and [9]School of Medicine, University of California Davis, Davis, CA, USA. [3]World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, and [4]Dept of Biomedical Sciences, University of Sassari, Sassari, Italy. [5]Médecins Sans Frontières, Cape Town, South Africa. [6]US Centers for Disease Control and Prevention, HIV/STD Research Program, Bangkok, Thailand. [10]Clinical Infectious Diseases, Tuberculosis Center Borstel, Borstel, Germany. [11]Dept of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, and [7]Montreal Chest Institute, McGill University, Montreal, QC, Canada. [12]A full list of the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB members and their affiliations can be found in the Acknowledgements.

**Correspondence:** D. Menzies, Montréal Chest Institute, 3650 St Urbain St., Montréal, PQ, H2X 2P4, Canada. E-mail: Dick.Menzies@McGill.ca

ABSTRACT A meta-analysis for response to treatment was undertaken using individual data of multidrug-resistant tuberculosis (MDR-TB) (resistance to isoniazid and rifampicin) patients from 26 centres. The analysis assessed the impact of additional resistance to fluoroquinolones and/or second-line injectable drugs on treatment outcome.

Compared with treatment failure, relapse and death, treatment success was higher in MDR-TB patients infected with strains without additional resistance (n=4763; 64%, 95% CI 57–72%) or with resistance to second-line injectable drugs only (n=1130; 56%, 95% CI 45–66%), than in those having resistance to fluoroquinolones alone (n=426; 48%, 95% CI 36–60%) or to fluoroquinolones plus second-line injectable drugs (extensively drug resistant (XDR)-TB) (n=405; 40%, 95% CI 27–53%). In XDR-TB patients, treatment success was highest if at least six drugs were used in the intensive phase (adjusted OR 4.9, 95% CI 1.4–16.6; reference fewer than three drugs) and four in the continuation phase (OR 6.1, 95% CI 1.4–26.3). The odds of success in XDR-TB patients was maximised when the intensive phase reached 6.6–9.0 months duration and the total duration of treatment 20.1–25.0 months.

In XDR-TB patients, regimens containing more drugs than those recommended in MDR-TB but given for a similar duration were associated with the highest odds of success.

All data were from observational studies and methodologies varied between centres, therefore, the bias may be substantial. Better quality evidence is needed to optimise regimens.

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## Introduction

The emergence of drug resistance among tuberculosis (TB) strains was first reported >60 years ago, soon after the introduction of the first antibiotics to treat TB [1–3]. Since then, broader patterns of drug resistance have been described worldwide, with the highest levels of resistance among TB patients being recorded in recent years [4]. In Belarus and other countries of the former Soviet Union, more than one-quarter of treatment-naïve TB patients, and well over half of those who were previously treated, are now infected with strains resistant to both rifampicin and isoniazid (multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB)) [5]. In 2010, there were an estimated 12 million prevalent TB cases globally, of which ~650 000 were infected with MDR-TB strains. China and India are each estimated to have >60 000 MDR-TB cases emerging annually from among the pulmonary TB patients that these countries notify [6]. Surveillance data from a number of settings indicate that, on average, 9.4% (95% CI 7.4–11.6%) of MDR-TB strains have additional resistance to both fluoroquinolones and second-line injectable drugs, *i.e.* extensively drug resistant (XDR)-TB [7]. The first reported outbreak of XDR-TB, which occurred in a high HIV-prevalence setting, was characterised by very high mortality [8]. Subsequent reports have confirmed that treatment outcomes for XDR-TB are generally worse than MDR-TB [9]. There is less information about the influence of individual resistance to fluoroquinolones and to second-line injectable drugs on prognosis in MDR-TB patients [10].

Treatment of MDR-TB is difficult. Current regimens, when compared to those used to treat drug-susceptible TB, are less effective but more costly, toxic and lengthy [11, 12]. Because there are no published randomised trials on the treatment of MDR-TB patients, the evidence supporting current recommendations is of low quality and based largely on observational studies [13]. This leads to considerable controversy regarding optimal treatment. There is even less evidence regarding treatment of patients with more advanced patterns of resistance, such as XDR-TB. As a result, the current World Health Organization (WHO) treatment recommendations for XDR-TB patients are based on expert opinion alone [11].

We conducted an individual patient data meta-analysis to explore the effect of patient characteristics, regimen composition and duration on treatment outcomes for MDR-TB patients grouped according to whether their infecting strains had additional resistance to either fluoroquinolones or second-line injectable drugs, or both (XDR-TB).

## Methods

### *Data collection*

The collection and analysis of the individual patient data was conducted to address specific questions developed by an expert guideline development group convened by the WHO to revise recommendations for treatment of drug-resistant TB [13]. The study was approved by the ethics review board committees of the Montréal Chest Institute and McGill University Health Centre (Montréal, Canada) and the local ethics review boards of participating centres, when necessary. The study was determined to be research not involving identifiable human subjects by the USA Centers for Disease Control and Prevention, because anonymised data originally collected for a different purpose were used.

The studies included in the individual patient data meta-analysis were identified from original studies published in three recent systematic reviews of MDR-TB treatment outcomes in MDR-TB patients [14–16]. These reviews searched the EMBASE and MEDLINE databases, the Cochrane Library and the ISI Web of Science, and included studies published after 1970 that reported original data with at least one treatment outcome that conformed with agreed definitions [17] for patients with bacteriologically confirmed MDR-TB. All studies identified were from observational studies of patient groups; none were randomised trials. Most patients were treated with individualised regimens in specialised referral centres.

The additional inclusion criteria for this meta-analysis were that the study authors could be contacted; that they were willing to share their data; and that the cohort included ⩾25 MDR-TB patients. Anonymised

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information provided included patient demographics (age and sex), clinical features (site of disease, pretreatment sputum smear results for acid-fast bacilli and culture, chest radiography, HIV infection, use of antiretroviral therapy (ART)), drug susceptibility test (DST) results (initial DST to all first- and second-line drugs used), treatment factors (drugs and duration for initial and continuous phases of treatment, and surgical resection) and treatment outcomes, including adverse events. Individual patients were excluded from the datasets if they had only extrapulmonary TB or were missing information on drug regimens received or on treatment outcome. We included only patients for whom DST results for at least one fluoroquinolone and one second-line injectable drug were available. Most centres tested for susceptibility to either amikacin or kanamycin; this analysis grouped resistance to these two aminoglycosides into one variable. In this study, amikacin, kanamycin and capreomycin, but not streptomycin, were considered second-line injectable drugs. The term macrolide refers to azithromycin, clarithromycin or roxithromycin. Later-generation fluoroquinolones refer to gatifloxacin, levofloxacin, moxifloxacin and sparfloxacin. Low-dose levofloxacin refers to a daily administration of $<$750 mg. The drugs belonging to group 4 and group 5 used in patients included in this study are listed in online supplementary table S1 (data from [18]).

### Data analysis

The methodology used for conducting the individual patient data meta-analysis was based on criteria established by the Cochrane collaboration [19], and is described in greater detail elsewhere [20]. We considered three elements of drug-exposure in our analysis: 1) individual drugs administered; 2) number of likely effective drugs used; and 3) duration of treatment regimen. A drug was considered as likely to be effective if DST results showed the strain to be susceptible. If a medication was reported as having been used at any time during treatment, then the patient was considered to have been exposed to the particular drug. The intervals used to analyse the duration of treatment (intensive phase and total) provided for a sizeable number of cases to be present in each of the subgroups.

We first estimated pooled proportions of cases with different drug resistance patterns using an across-centre binomial random effects meta-analysis (PROC NLMIXED in SAS version 9.2; SAS Institute, Cary, NC, USA). For the individual patient data meta-analysis we used random effects multivariable logistic regression (random intercept and random slope) with penalised quasi-likelihood in order to evaluate the impact of drug-exposure on treatment outcomes (using PROC GLIMMIX in SAS) [21–23]. Estimates were adjusted for five covariates: age, sex, HIV infection, extent of disease (a composite covariate scored by merging sputum-smear positivity and cavities on chest radiography) and previous history of TB treatment (which was a three-level variable: no previous TB treatment, previous TB treatment with first-line drugs and previous MDR-TB treatment with second-line drugs). Missing values were imputed for the five covariates used in multivariable analyses. For imputation we used the mean from the other members of the same cohort to which the individual belonged if more than half the cohort members had values for that variable, or the mean value from all individuals analysed. Adjusted odds ratios and their confidence intervals were used to report the associations between patient characteristics and outcomes in the different patient groups.

Treatment success was defined as cure or treatment completion [17] and was compared with 1) treatment failure, relapse or death for the analysis of individual drugs and number of drugs; and 2) failure or relapse for the analysis of duration of treatment. Patients who died or defaulted were not considered in the analysis on treatment duration because a number of studies recorded the actual rather than the planned length of treatment and, consequently, the duration was shortened by death or default.

## Results

### Study centres and patient characteristics

Individual data from MDR-TB patients in 31 centres were available for the analysis [24–55] (online supplementary table S2). Five centres did not have information about DST results for fluoroquinolones and/or second-line injectable drugs. In total, 6724 MDR-TB cases from the other 26 centres were included in the analysis. Patients were placed on treatment in the various cohorts between 1980 and 2009. 22 centres reported at least one case of MDR-TB plus resistance to at least one second-line injectable drug only (MDR-TB+INJr), 18 reported cases with MDR-TB plus fluoroquinolone resistance only (MDR-TB+FQr) and 17 centres had XDR-TB cases. The size of the cohorts in each centre ranged from one to 1786 MDR-TB cases. Overall, 4763 (71%) patients had MDR-TB but were susceptible to both fluoroquinolones and second-line injectable drugs (MDR-TB only), 1130 (17%) had MDR-TB+INJr, 426 (6%) had MDR-TB+FQr and 405 (6%) had XDR-TB.

The 6724 MDR-TB subjects had a mean $\pm$ SD age of $39.5 \pm 13.5$ years, 69% were male, 70% had been treated previously for TB (60% with first-line and 10% with second-line drugs) and 11% were HIV-infected (table 1). The age and sex profile was comparable between the patient groups. HIV infection was less frequent in MDR-TB+FQr (1.7%) and MDR-TB+INJr (5.1%) than in MDR-TB only patients (14%). Fewer

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TABLE 1 Characteristics of multidrug-resistant tuberculosis (MDR-TB) patients with different resistance patterns of *Mycobacterium tuberculosis*

| | MDR-TB only | MDR-TB+INJr | MDR-TB+FQr | XDR-TB | Total MDR-TB cases |
|---|---|---|---|---|---|
| **Studies n** | 26 | 22 | 18 | 17 | 26 |
| **Cases n** | 4763 | 1130 | 426 | 405 | 6724 |
| **Demographic characteristics** | | | | | |
| Age years | 39.2±13.5 | 39.9±13.3 | 41.6±14.3 | 40.6±13.8 | 39.5±13.5 |
| Male | 68 | 74 | 68 | 67 | 69 |
| HIV-infected | 14 | 5.1 | 1.7 | 3.7 | 11 |
| **Clinical characteristics** | | | | | |
| Pulmonary TB only | 97 | 97 | 96 | 97 | 97 |
| Sputum-smear positive | 73 | 73 | 79 | 79 | 74 |
| Cavities on chest radiography | 65 | 66 | 60 | 77 | 66 |
| Extensive disease# | 72 | 71 | 78 | 78 | 73 |
| Previous TB treatment¶ | | | | | |
| None | 20 | 24 | 19 | 16 | 30 |
| First-line drugs only | 73 | 60 | 64 | 57 | 60 |
| Second-line drugs for MDR-TB | 7 | 16 | 17 | 27 | 10 |
| Had a serious adverse event during therapy | 29 | 47 | 33 | 43 | 32 |

Data are presented as mean±SD or %, unless otherwise stated. Values shown were computed using simple pooling across all studies. Percentages were calculated on the number of patients in each group with information available. MDR-TB: multidrug-resistant TB (resistance to at least isoniazid and rifampicin); MDR-TB only: MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested); MDR-TB+INJr: MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones; MDR-TB+FQr: MDR-TB plus resistance to any fluoroquinolone, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)). #: Extensive disease was defined as sputum-smear positive, or cavities on chest radiography if information about sputum-smear was missing. ¶: Previous tuberculosis (TB) treatment was defined as treatment with any TB drug for ⩾=1 month. Previous treatment could be with first-line drugs or with ⩾2 second-line drugs for MDR. In some patients, information was only available that they had been treated previously for TB, but not whether this was with first- or second-line drugs.

than 10 HIV infected patients received ART in total. XDR-TB cases were more likely to have cavities on chest radiography and to have been treated with second-line drugs than the other MDR-TB patients.

### Resistance patterns

The majority of centres tested for susceptibility to a single fluoroquinolone, mostly ofloxacin, and very few for later-generation fluoroquinolones. Over 3000 patients had resistance to streptomycin, representing 61% of all those tested (table 2). Prevalence of streptomycin resistance was highest among patients with resistance to second-line injectable drugs (*i.e.* XDR-TB or MDR-TB+INJr). Resistance to both a second-line aminoglycoside (amikacin and/or kanamycin) and capreomycin occurred in 13% of all patients, 30% of XDR-TB and 33% of MDR-TB+INJr. More than 90% of XDR-TB patients had strains resistant to six or more anti-TB drugs.

### Outcomes

Overall, 62% of patients were successfully treated, in 7% treatment failed or the patient relapsed, 9% died and 17% defaulted (table 3). XDR-TB cases had the lowest rates of treatment success and the highest rates of failure, relapse and death. After adjustment for patient clinical characteristics and clustering by centres, treatment success was significantly lower in all three MDR-TB patient groups with additional resistance (table 4). Treatment success declined as drug resistance patterns advanced; the lowest odds of treatment success were seen with XDR-TB and were next lowest in patients with MDR-TB+FQr (fig. 1). Treatment success was also less likely in patients who were older, had more advanced disease, were HIV-infected or had a history of prior TB treatment, especially with second-line drugs.

### Treatment correlates with outcomes

#### Specific drugs and regimens

Treatment regimens included ethambutol in 44% of all patients and pyrazinamide in 67% of all patients; over 85% received an injectable drug (in 14% streptomycin only). Almost 90% of patients received a fluoroquinolone, but in only 5% was this a later-generation fluoroquinolone (online supplementary table S1). Fluoroquinolones were used less often if resistance to them was detected (73–76% *versus* 91–92%

TABLE 2 Resistance to anti-tuberculosis drugs by multidrug-resistant tuberculosis (MDR-TB) patient group

| | MDR-TB only | MDR-TB +INJr | MDR-TB +FQr | XDR-TB | Total MDR-TB cases |
|---|---|---|---|---|---|
| **Cases n** | 4763 | 1130 | 426 | 405 | 6724 |
| **Resistance** | | | | | |
| First-line drugs | | | | | |
| Pyrazinamide | 1052 (41) | 556 (70) | 234 (58) | 211 (69) | 2053 (50) |
| Ethambutol | 1524 (51) | 845 (76) | 296 (74) | 295 (81) | 2960 (61) |
| Fluoroquinolones[#] | 0 | 0 | 426 (100) | 405 (100) | 831 (12) |
| Injectable drugs | | | | | |
| Streptomycin | 1534 (51) | 960 (86) | 226 (53) | 291 (78) | 3011 (61) |
| Amikacin/kanamycin[¶] | 0 | 1042 (92) | 0 | 383 (95) | 1425 (21) |
| Capreomycin | 0 | 399 (42) | 0 | 104 (38) | 503 (16) |
| Amikacin/kanamycin and capreomycin | 0 | 311 (33) | 0 | 82 (30) | 393 (13) |
| Amikacin/kanamycin and capreomycin and streptomycin | 0 | 295 (31) | 0 | 68 (25) | 363 (12) |
| Group 4 drugs | | | | | |
| Ethionamide/protionamide | 528 (19) | 401 (41) | 194 (48) | 212 (59) | 1335 (29) |
| Cycloserine/terizidone | 125 (4) | 56 (5) | 76 (18) | 89 (24) | 346 (7) |
| *p*-aminosalicylic acid | 391 (14) | 281 (31) | 125 (31) | 127 (43) | 924 (21) |
| **TB drugs tested**[+] | 7.9±3.0 | 10.0±1.3 | 10.2±0.9 | 9.6±1.7 | 8.5±2.1 |
| **Total number of TB drugs to which strain was resistant**[§] | | | | | |
| 2 | 2259 (47) | 0 | 0 | 0 | 2259 (34) |
| 3 | 947 (20) | 15 (1) | 19 (4) | 0 | 981 (15) |
| 4 | 784 (16) | 100 (9) | 66 (15) | 4 (1) | 954 (14) |
| 5 | 513 (11) | 331 (29) | 101 (24) | 32 (8) | 977 (15) |
| 6 | 209 (4) | 296 (26) | 118 (28) | 108 (27) | 731 (11) |
| 7 | 42 (1) | 221 (20) | 89 (21) | 105 (26) | 457 (7) |
| 8 | 9 (0.2) | 128 (11) | 25 (6) | 75 (19) | 237 (4) |
| 9 | 0 | 37 (3) | 8 (2) | 46 (11) | 91 (1) |
| ⩾10 | 0 | 2 (0.2) | 0 | 35 (9) | 37 (0.3) |

Data are presented as n, n (%) or mean±SD. Drug-susceptibility test results for Group 5 drugs were available from very few centres and were not analysed. n (%) data are presented for the number of cases whose isolate was tested to that specific drug. All cases were tested for susceptibility to at least one fluoroquinolone (FQ) and one second-line injectable drug, but not all the other drugs. #: Most centres tested only for resistance to ofloxacin. Very few centres also tested for resistance to later-generation FQs (results of these tests are not shown). By definition, two patient groups were susceptible to FQ. ¶: Resistance to amikacin or kanamycin combined. Most centres tested for susceptibility to only one of these two drugs and considered them cross-resistant. +: Includes tests to isoniazid and rifampin, as well as to FQs and second-line injectable drugs (performed in all cases). §: In addition to isoniazid and rifampin, to which all patients were resistant, being MDR-TB. MDR-TB: multidrug-resistant tuberculosis (resistance to at least isoniazid and rifampicin); MDR-TB only: MDR-TB, but susceptible to FQs, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested); MDR-TB+INJr: MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to FQs; MDR-TB+FQr: MDR-TB plus resistance to any FQ, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any FQ and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)).

if susceptible). Capreomycin was given more often than amikacin/kanamycin to patients with MDR-TB+INJr (56% *versus* 22%) and XDR-TB (40% *versus* 33%). Almost 95% of patients in each subgroup received at least one group 4 drug, usually ethionamide or protionamide. Cycloserine or terizidone were given more often when MDR-TB patients had strains with additional resistance (84–89% *versus* 58%), as was *p*-aminosalicylic acid (46–64% *versus* 35%). Group 5 drugs were also used more frequently in the MDR-TB patients with additional resistance (36–44%) than those without (18%). 6% of all patients had adjunctive lung resection surgery; this was most frequent in patients with MDR-TB+FQr (online supplementary table S1).

Table 5 summarises the association of individual anti-TB drugs with treatment success compared to failure, relapse or death in the different MDR-TB patient groups. No drug was statistically significantly associated with treatment success among the MDR-TB+FQr or XDR-TB groups. In the MDR-TB+INJr group, amikacin or kanamycin (over streptomycin) and ethionamide or protionamide were significantly associated with treatment success. In the MDR-TB only patient group, the use of amikacin or kanamycin,

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TABLE 3 Treatment outcomes by multidrug-resistant tuberculosis (MDR-TB) patient group

| Pooled treatment outcomes# | MDR-TB only | MDR-TB +INJr | MDR-TB +FQr | XDR-TB | Total |
|---|---|---|---|---|---|
| **Subjects** | 4763 | 1130 | 426 | 405 | 6724 |
| **Treatment success** | 64 (57–72) | 56 (45–66) | 48 (36–60) | 40 (27–53) | 62 (54–69) |
| **Treatment failure or relapse** | 4 (2–6) | 12 (9–15) | 18 (14–21) | 22 (15–28) | 7 (4–9) |
| **Died** | 8 (5–11) | 8 (3–14) | 11 (3–19) | 15 (8–23) | 9 (5–12) |
| **Defaulted** | 18 (12–24) | 16 (7–24) | 12 (1–23) | 16 (8–24) | 17 (11–22) |

Data are presented as n or % (95% CI). MDR-TB: multidrug-resistant TB (resistance to at least isoniazid and rifampicin); MDR-TB only: as MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested); MDR-TB+INJr: MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones; MDR-TB+FQr: MDR-TB plus resistance to any fluoroquinolone, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)). #: from study level meta-analysis; column percentages do not total 100%. See the Methods section and [17] for treatment outcome definitions.

capreomycin, ofloxacin, ethionamide or protionamide and cycloserine were all associated with significantly higher odds of treatment success. Conversely, those patients in this group who received two group 5 drugs had a lower likelihood of treatment success than those receiving one group 5 drug, and so did those on a regimen without a fluoroquinolone or which contained only first-line drugs (online supplementary table S3). MDR-TB+INJr patients treated with a capreomycin-containing regimen fared worse than those who received kanamycin alone.

TABLE 4 Association of treatment success with patient characteristics and multidrug-resistant tuberculosis (MDR-TB) patient group

| | Cases | Adjusted odds of treatment success *versus* treatment failure/relapse/death# |
|---|---|---|
| **Male (*versus* female)¶** | 4653 | 1.0 (0.9–1.1) |
| **Older age (per 10-year increment) ¶** | 6724 | **0.8 (0.8–0.9)** |
| **HIV infected (*versus* not HIV infected) ¶** | 615 | **0.3 (0.2–0.4)** |
| **Extensive disease (*versus* not extensive) ¶** | 4792 | **0.5 (0.4–0.6)** |
| **Previous TB treatment¶** | | |
| None | 1275 | 1.0 (Reference) |
| First-line drugs only | 4410 | **0.6 (0.5–0.8)** |
| First-line and second-line drugs | 618 | **0.2 (0.15–0.3)** |
| **MDR-TB patient group+** | | |
| MDR-TB only | 4763 | 1.0 (Reference) |
| MDR+INJr | 1130 | **0.6 (0.5–0.7)** |
| MDR+FQr | 426 | **0.3 (0.2–0.4)** |
| XDR-TB | 405 | **0.2 (0.2–0.3)** |
| **Pulmonary resection surgery performed (*versus* no pulmonary resection surgery)+** | 373 | 1.5 (0.9–2.6) |
| **Experienced a serious adverse event (*versus* no serious adverse event)+** | 1511 | 1.0 (0.8–1.2) |

Data are presented as n or adjusted OR (95% CI). TB: tuberculosis; MDR-TB: multidrug-resistant TB (resistance to at least isoniazid and rifampicin); MDR-TB only: MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested); MDR-TB+INJr: MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones; MDR-TB+FQr: MDR-TB plus resistance to any fluoroquinolone, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)). #: odds ratios of treatment success (cure and completion) *versus* treatment failure/relapse/death adjusted for age, sex, HIV infection, previous TB treatment, previous MDR treatment (treatment for $>1$ month with two or more second-line drugs) and extent of disease. See Methods and [17] for treatment outcome definitions. ¶: estimate adjusted for all other covariates (characteristics) shown. +: each of these parameters estimated separately, and adjusted for age, sex, HIV, extent of disease and previous treatment with first- or second-line TB drugs. Statistical significance is represented by bold type.

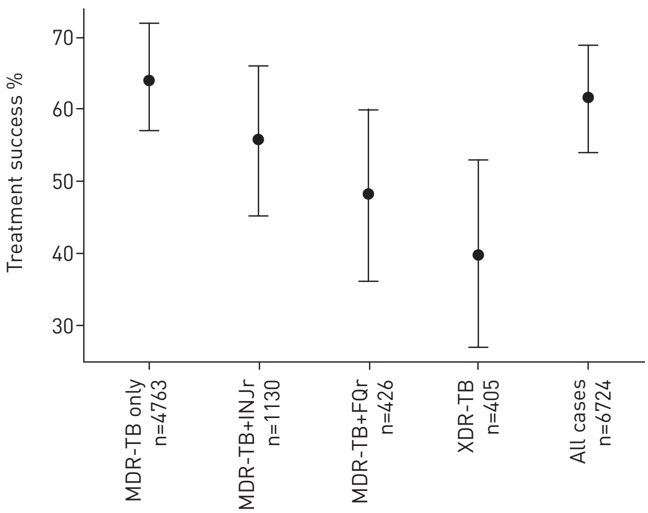


FIGURE 1 Treatment success among different multidrug-resistant tuberculosis (MDR-TB) patient groups. Data are presented as point estimates and 95% CI. MDR-TB+INJr: MDRTB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones; MDR-TB+FQr: MDR-TB plus resistance to any fluoroquinolone, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)).

### *Number of drugs and duration of treatment*

XDR-TB patients who in the intensive phase received six or more drugs, which were likely to be effective, and MDR-TB only patients who received four drugs, had a higher likelihood of treatment success than patients receiving fewer drugs (table 6). In the continuation phase, the use of four drugs for XDR-TB patients and three drugs for MDR-TB patients without fluoroquinolone-resistant strains were associated with the highest odds of treatment success.

Among all patients except those in the MDR-TB+FQr group, an intensive phase duration of 6.6–9.0 months was associated with the maximal odds of treatment success (statistically significant) compared with patients treated for shorter or longer durations (table 7). The odds of treatment success in the same three patient groups peaked when total duration of treatment was 20.1–25.0 months.

## Discussion

We found a stepwise worsening of treatment outcomes in MDR-TB cases treated in multiple centres as the resistance pattern of infecting TB strains advanced from MDR without additional resistance, to added resistance to a second-line injectable drug, to resistance to a fluoroquinolone, and then to both (XDR-TB). This effect is attributable to the gradual loss of effectiveness of the two classes of medications that form the backbone of MDR-TB treatment. The negative impact on treatment success when isoniazid and rifampicin are lost to resistance was demonstrated several years ago [56]. Our findings complement those from published work on separate patient cohorts, which showed that resistance to fluoroquinolones or second-line injectable drugs in MDR-TB patients was associated with poorer prognosis [57, 58] and that outcomes for patients with XDR-TB are particularly unfavourable [8–10, 35, 40].

Current treatment guidelines for MDR-TB recommend the use of pyrazinamide along with at least four second-line TB medications likely to be effective given *in vitro* susceptibility results and prior treatment history [13]. A typical regimen can be created using a fluoroquinolone, a second-line aminoglycoside or capreomycin, ethionamide or protionamide and cycloserine or terizidone or *p*-aminosalicylic acid. With resistance to either fluoroquinolones or second-line injectable drugs, a regimen of four effective drugs is still possible without using any of the group 5 medications, most of which have uncertain activity against TB. However, with resistance to both of these drug classes, it becomes difficult to construct a tolerable regimen containing a sufficient number of effective drugs [11]. This difference in ability to create a robust treatment regimen may explain why treatment outcomes are so low in the XDR-TB group. The results of our meta-analysis indicate that in XDR-TB patients a regimen of a similar duration, but composed of more drugs than the regimen recommended for MDR-TB patients without additional resistance is more likely to achieve success [20].

In our study, we found that approximately one-third of patients tested for resistance to both the second-line aminoglycosides and capreomycin were resistant to drugs from both classes. This finding may suggest cross-resistance between these drug classes, which has been described, but is known not to be complete and is, therefore, less frequent [59]. However, it could also be explained by previous exposure


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TABLE 5 Association of treatment success with individual drugs used in treatment by multidrug-resistant tuberculosis (MDR-TB) patient group

| | MDR-TB only | | MDR-TB+INJr | | MDR-TB+FQr | | XDR-TB | |
|---|---|---|---|---|---|---|---|---|
| | Cases[#] n | Adjusted OR (95% CI)[¶] | Cases[#] n | Adjusted OR (95% CI)[¶] | Cases[#] n | Adjusted OR (95% CI)[¶] | Cases[#] n | Adjusted OR (95% CI)[¶] |
| **First-line drugs** | | | | | | | | |
| Pyrazinamide | 2480 | 1.3 (0.8–2.0) | 474 | 1.2 (0.8–1.8) | 171 | 0.8 (0.4–1.5) | 174 | 1.1 (0.6–2.0) |
| Ethambutol | 1794 | **0.7 (0.5–0.9)** | 271 | 0.8 (0.6–1.2) | 94 | 0.7 (0.4–1.3) | 93 | 1.8 (0.9–3.5) |
| **Injectable drugs[+]** | | | | | | | | |
| Amikacin or kanamycin | 2250 | | 153 | | 135 | | 85 | |
| *versus* no injectable drug | | **1.9 (1.1–3.1)** | | 2.0 (0.7–5.4) | | 0.8 (0.1–5.6) | | 2.0 (0.5–8.7) |
| *versus* capreomycin | | 1.1 (0.6–1.9) | | 1.8 (0.9–3.6) | | 1.1 (0.2–5.9) | | 1.2 (0.3–5.3) |
| *versus* streptomycin | | 1.4 (0.9–2.3) | | **2.4 (1.1–5.0)** | | 1.1 (0.3–4.3) | | 1.7 (0.3–7.9) |
| Capreomycin only | 204 | | 435 | | 34 | | 109 | |
| *versus* no injectable drug | | **2.2 (1.1–4.2)** | | 0.9 (0.2–4.1) | | | | 2.5 (0.9–7.0) |
| *versus* streptomycin | | 1.4 (0.6–3.3) | | 0.8 (0.2–3.9) | | | | 1.4 (0.1–14) |
| **Fluoroquinolones[§]** | | | | | | | | |
| Ofloxacin | 2956 | | 787 | | 197 | | 227 | |
| *versus* no fluoroquinolone | | **2.9 (1.7–4.9)** | | 2.8 (0.9–8.6) | | 1.1 (0.5–2.4) | | 0.7 (0.3–1.6) |
| *versus* ciprofloxacin | | 1.2 (0.5–3.2) | | 1.8 (0.1–23) | | 1.0 (0.1–19) | | 0.2 (0.1–3.6) |
| **Group 4 drugs** | | | | | | | | |
| Ethionamide or protionamide | 2973 | **2.2 (1.5–3.2)** | 689 | **1.6 (1.0–2.4)** | 258 | 0.8 (0.4–1.7) | 253 | 1.0 (0.5–2.1) |
| Cycloserine or terizidone | 2007 | **1.8 (1.4–2.2)** | 822 | 1.7 (0.8–3.9) | 292 | 0.9 (0.3–3.0) | 284 | 1.3 (0.5–3.6) |
| *p*-aminosalicylic acid | 1396 | 1.0 (0.8–1.3) | 614 | 1.1 (0.7–1.6) | 219 | 1.1 (0.6–2.3) | 228 | 1.3 (0.6–3.1) |
| **Group 5 drugs[ƒ]** | | | | | | | | |
| Any one group 5 drug *versus* none | 561 | 0.8 (0.6–1.2) | 323 | 0.9 (0.5–1.6) | 84 | 0.6 (0.3–1.4) | 95 | 1.1 (0.4–2.9) |
| Two or more group 5 drugs *versus* one | 135 | **0.5 (0.2–0.9)** | 111 | 0.6 (0.3–1.5) | 55 | 0.8 (0.3–1.8) | 58 | 1.2 (0.5–3.3) |

MDR-TB: multidrug-resistant TB (resistance to at least isoniazid and rifampicin); MDR-TB only: MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested); MDR-TB+INJr: MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones; MDR-TB+FQr: MDR-TB plus resistance to any fluoroquinolone, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)). [#]: number of cases that received the drug in question and were included in the specific analysis. [¶]: odds ratios of treatment success (cure and completion) *versus* treatment failure/relapse/death adjusted for age, sex, HIV infection, previous TB treatment, previous MDR treatment (treatment for >1 month with two or more second-line drugs) and extent of disease. If there were <50 observations no estimate was derived. See Methods and [17] for treatment outcome definitions. [+]: patients receiving two or more injectable drugs were excluded from this analysis. [§]: patients receiving two or more fluoroquinolones were excluded from this analysis. Insufficient numbers of patients received later-generation fluoroquinolones (including gatifloxacin, levofloxacin, moxifloxacin and sparfloxacin) within the MDR-TB patient groups with additional resistance, so were not analysed. [ƒ]: insufficient numbers of patients received specific group 5 drugs within the MDR-TB patient groups with additional resistance, so outcomes by individual group 5 drugs were not analysed. Group 5 drugs included amoxicillin/clavulanate, macrolides (azithromycin, clarithromycin and roxithromycin), clofazimine, thiacetazone, imipenem, linezolid, high-dose isoniazid and thioridazine. Statistical significance is represented by bold type.

to both types of injectable drugs or to primary infection with a strain bearing this resistance pattern. Centres may use capreomycin empirically to treat cases with strains resistant to second-line aminoglycosides without the capacity to test for resistance to this drug. A number of patients received more than one type of injectable drug, but these were received sequentially, mostly because of DST results indicating resistance to the first injectable drug. Our findings suggest that capreomycin would probably not benefit such patients and could cause more harm than good, given the known toxicity of this agent. Patients on second-line medications often experience serious adverse events that require a change in therapy [60]. In our series an adverse event leading to a change in therapy occurred in 32% of cases overall.

Another important observation was that among patients with strains resistant to fluoroquinolones, second-line injectable drugs, or both, only one-quarter had been treated previously with second-line TB drugs. The rest were treated with first-line drugs or were never treated at all. This suggests that many of the MDR-TB cases with strains bearing additional resistance are due to primary infection with a resistant strain and, by inference, that the acquisition of drug resistance by a strain does not necessarily compromise its transmissibility [61]. Moreover, the propensity for XDR-TB strains to cause epidemics has been well recognised, particularly in settings with high HIV prevalence [8]. This finding reinforces the importance of having a comprehensive infection control component in all TB control programmes. Treatment of drug-resistant TB patients with adequate regimens should also be instituted earlier, and scaled up globally to cover many more patients than the minority who are currently on appropriate treatment, particularly in high-burden settings [6, 62, 63]. In 2010, only 16% of MDR-TB cases estimated to occur among TB patients notified worldwide were reported to have been started on treatment. Moreover, the early use of ART in HIV-infected patients with MDR-TB is very important [13].

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TABLE 6 Association of treatment success with the number of effective drugs used in the intensive and continuation phases of treatment by the multidrug-resistant tuberculosis (MDR-TB) patient group

| Number of drugs | MDR-TB only | | MDR-TB+INJr | | MDR-TB+FQr | | XDR-TB | |
|---|---|---|---|---|---|---|---|---|
| | Cases n | Adjusted OR# (95% CI) | Cases n | Adjusted OR# (95% CI) | Cases n | Adjusted OR# (95% CI) | Cases n | Adjusted OR# (95% CI) |
| **Intensive phase¶** | | | | | | | | |
| ⩽2 | 45 | 1.0 (reference) | 29 | 1.0 (reference) | 10 | 1.0 (reference) | 24 | 1.0 (reference) |
| 3 | 62 | 1.1 (0.5–2.3) | 27 | 1.7 (0.5–5.2) | 32 | 1.0 (reference) | 47 | 1.0 (reference) |
| 4 | 165 | **1.9 (1.0–3.7)** | 83 | 1.3 (0.5–3.1) | 49 | 1.6 (0.7–3.8) | 46 | 1.9 (0.8–4.3) |
| 5 | 296 | 1.7 (0.8–3.8) | 137 | 1.2 (0.4–3.4) | 35 | 1.4 (0.3–6.4) | 36 | 1.8 (0.5–6.6) |
| ⩾6 | 380 | 1.0 (0.5–1.8) | 120 | 1.3 (0.5–3.3) | 27 | 1.1 (0.4–2.9) | 20 | **4.9 (1.4–16.6)** |
| **Continuation phase+** | | | | | | | | |
| ⩽2 | 77 | 1.0 (reference) | 46 | 1.0 (reference) | 35 | 1.0 (reference) | 27 | 1.0 (reference) |
| 3 | 133 | **5.9 (3.1–11.0)** | 33 | **12.2 (3.4–44)** | 27 | 2.5 (0.8–7.4) | 32 | 3.3 (1.3–8.5) |
| 4 | 239 | 6.0 (2.8–13.1) | 101 | 3.7 (1.7–8.2) | 27 | 3.1 (0.5–21.1) | 28 | **6.1 (1.4–26.3)** |
| ⩾5 | 233 | 4.7 (2.7–8.1) | 100 | 3.1 (1.7–6.0) | 20 | 2.3 (0.7–7.2) | 17 | 2.3 (0.7–7.6) |

MDR-TB: multidrug-resistant TB (resistance to at least isoniazid and rifampicin); MDR-TB only: MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested); MDR-TB+INJr: MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones; MDR-TB+FQr: MDR-TB plus resistance to any fluoroquinolone, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)). #: odds ratios of treatment success (cure and completion) *versus* treatment failure/relapse/death adjusted for age, sex, HIV infection, previous TB treatment, previous MDR treatment (treatment for >1 month with two or more second-line drugs) and extent of disease. See Methods and [17] for treatment outcome definitions. ¶: the initial part of a course of treatment during which an injectable drug is given. +: the period immediately following the initial phase when no injectable drug is given. Only 18 studies provided information regarding drug susceptibility testing and the number of drugs in the intensive phase, while only 15 of these described the number of drugs in the continuation phase. Statistical significance is represented by bold type.

This study represents the largest known individual patient data meta-analysis for outcomes of MDR-TB cases with strains harbouring additional resistance. Patients were treated in multiple settings (online supplementary table S2), located in many countries and in all WHO regions, thus enhancing the generalisability of the findings. Detailed data, which were standardised as much as possible, were available for all cases. Differences in treatment regimens often reflected differences in treating physicians' opinions and past experiences. Hence this dataset included substantial variation in the approach to treatment, independent of differences in patient characteristics. We had the opportunity to examine how treatment correlates with outcomes, which would not be possible with single-centre reports.

Nevertheless, this study does suffer from a number of important limitations. While attempts were made to standardise the variables, residual heterogeneity in prior treatment for TB, diagnostic methods, additional drug resistance, drug quality, treatment regimens, drug dosages, frequency of administration and use of thoracic surgery complicate the pooling of observations. DST results to ethambutol, pyrazinamide and the group 4 drugs are known to be less accurate and reproducible than those for the drugs that define XDR-TB. As none of the studies were randomised controlled trials, substantial bias and confounding are expected and the quality of evidence would be considered low [64]. Patients with more advanced disease, or infected with strains having broader resistance and with a considerable previous treatment history may have been more likely to receive longer treatment with more drugs, since most of them received individualised regimens. Our findings that use of any group 5 drugs, or two group 5 drugs, were associated with worse treatment outcomes may reflect such bias, which cannot be adjusted for adequately in multivariable regression. Many of the patients with MDR-TB and fluoroquinolone resistance received early-generation fluoroquinolones, to which they were almost certainly resistant. Strains that develop resistance to early-generation fluoroquinolones may still show susceptibility to later-generation agents and DSTs to these agents should be performed, where possible [65]. The sparse use of later-generation fluoroquinolones may explain why no significant association was detected between their use and successful treatment outcome. Finally, most datasets lacked information on the timing of smear or culture conversion, which is considered useful in guiding the work of clinicians [11].


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TABLE 7 Association between the duration of treatment and treatment success by multidrug-resistant tuberculosis (MDR-TB) patient group

| | MDR-TB only | | MDR-TB+INJr | | MDR-TB+FQr | | XDR-TB | |
|---|---|---|---|---|---|---|---|---|
| | **Cases n** | **Adjusted OR# (95%CI)** | **Cases n** | **Adjusted OR# (95%CI)** | **Cases n** | **Adjusted OR# (95%CI)** | **Cases n** | **Adjusted OR# (95%CI)** |
| **Duration of intensive phase¶ months** | | | | | | | | |
| 1–4.0 | 1924 | 1.0 (reference) | 99 | 1.0 (reference) | 33 | 1.0 (reference) | 55 | 1.0 (reference) |
| 4.1–6.5 | 274 | 2.8 (0.8–9.7) | 82 | 3.2 (0.8–13.6) | 41 | 0.9 (0.2–4.5) | 41 | 6.1 (0.6–62) |
| 6.6–9.0 | 244 | **3.1 (1.1–8.3)** | 79 | **9.8 (1.9–49)** | 36 | 0.6 (0.1–4.1) | 37 | **71.0 (5.2–200)** |
| 9.1–20.0 | 347 | 2.1 (0.9–5.1) | 155 | 4.1 (1.5–11.2) | 55 | 0.4 (0.1–2.0) | 77 | 5.1 (1.2–21) |
| **Total duration of treatment months** | | | | | | | | |
| 6.0–15.0 | 443 | 1.0 (reference) | 279 | 1.0 (reference) | 54 | 1.0 (reference) | 87 | 1.0 (reference) |
| 15.1–20.0 | 2171 | 3.6 (1.7–7.9) | 260 | 3.1 (1.0–9.1) | 47 | 2.4 (0.4–14.3) | 79 | 2.0 (0.3–11.7) |
| 20.1–25.0 | 484 | **5.9 (3.0–11.5)** | 202 | **7.7 (3.8–15.7)** | 60 | 2.1 (0.7–6.5) | 61 | **5.5 (1.7–17.6)** |
| 25.1–30.0 | 147 | 2.8 (1.2–6.9) | 65 | 6.0 (2.3–15.6) | 24 | 4.1 (0.9–19.4) | 21 | 5.8 (1.3–25.1) |
| 30.1–36.0 | 61 | 1.8 (0.6–5.6) | 17 | 2.9 (0.7–12.2) | 13 | 1.1 (0.2–5.2) | 10 | 1.3 (0.2–7.8) |

MDR-TB: multidrug-resistant TB (resistance to at least isoniazid and rifampicin); MDR-TB only: MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested); MDR-TB+INJr: MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones; MDR-TB+FQr: MDR-TB plus resistance to any fluoroquinolone, but susceptible to amikacin/kanamycin and/or capreomycin (at least one second-line injectable drug tested); XDR-TB: extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug (amikacin/kanamycin and/or capreomycin)). #: Odds ratios of treatment success *versus* treatment failure or relapse adjusted for age, sex, HIV infection, previous TB treatment, previous MDR treatment (treatment for >1 month with two or more second-line drugs) and extent of disease. See Methods and [17] for treatment outcome definitions. ¶: The initial part of a course of treatment during which an injectable drug is given.

### Conclusions

This analysis adds evidence about the detrimental effect of escalating resistance on TB treatment outcomes. The findings regarding the number of drugs and duration of treatment should be of use to clinicians when treating patients with drug-resistant TB, but need to be interpreted with caution given the limitations mentioned. Randomised controlled trials are needed to optimise treatment regimens, including ancillary measures such as surgery. The addition of second-line drugs from the existent armamentarium of TB medications will only make a very modest difference once fluoroquinolones and second-line injectable agents are no longer an option. Better access for TB patients in resource-constrained settings to laboratories which can perform DST reliably, in order to detect resistance promptly, is very important [66]. New drugs that can be delivered in effective regimens are urgently needed to improve the outcomes of patients with the forms of drug-resistance described in this study [67].

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