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Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes

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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 to treatment failure, relapse and death, treatment success was higher in MDR-TB patients infected with strains without additional resistance (N=4763, 64% [95% confidence interval:57–72%]) or with resistance to second-line injectable drugs only (N=1130, 56% [45–66%]), than in those having resistance to fluoroquinolones alone (N=426, 48% [36–60%]) or to fluoroquinolones plus second-line injectable drugs (extensive drug resistance; XDR-TB) (N=405, 40% [27–53%]). In XDR-TB patients, treatment success was highest if at least 6 drugs were used in the intensive phase (adjusted OR: 4.9 [95%CI:1.4–16.6]; ref.<3 drugs) and 4 in the continuation phase (6.1 [1.4–26.3]). The odds of success in XDR-TB patients maximised as intensive phase reached 6.6–9.0 months duration and the total 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 bias may be substantial. Better quality evidence is needed to optimize regimens.

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Contributions

The data-collection, analyses and coordination of the Collaborative Group were undertaken by D.M. D.F and D.M. were responsible for the ideation of the study and the first draft of the text. N.G., G.B.M., G.S., H.C., T.H.H., M.G.H-D., S.K., K.D., R.C., L.D'A., C.L. and M.B. contributed to the restructuring and editing of the manuscript, and the selection of Tables to include. All authors agree with the contents of the manuscript.

Disclaimers

Dennis Falzon, Reuben M. Granich and Eva Nathanson are staff members of the World Health Organization (WHO). The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO. Timothy H. Holtz is a staff member of the U.S. Centers for Disease Control and Prevention (CDC). The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of CDC.

Keywords

Tuberculosis; Tuberculosis treatment; Drug resistance; Fluoroquinolone resistance; Injectable; Multidrug resistance; Extensively drug-resistant tuberculosis; Meta-analysis

Background

The emergence of drug-resistance among tuberculosis (TB) strains was first reported more than 60 years ago, soon after the introduction of the first antibiotics to treat TB (1), (2), (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 fourth of treatment-naïve TB patients, and well over a 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 about 650,000 were infected with MDR-TB strains. China and India are each estimated to have over 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. extensive drug resistance (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 randomized trials on the treatment of MDR-TB patients, the evidence supporting current recommendations is of low quality – 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 only on expert opinion(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 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, McGill University Health Centre, 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 U.S. Centers for Disease Control and Prevention because anonymized 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), (15), (16). These reviews searched 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 randomized trials. Most patients were treated with individualized regimens in specialized 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 at least 25 MDR-TB patients. Anonymized information provided included patient demographics (age and sex), clinical features (site of disease, pre-treatment 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, surgical resection), and treatment outcomes including adverse events. Individual patients were excluded from the datasets if they had only extra-pulmonary 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 article, 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 less than 750mg. The drugs belonging to Group 4 and Group 5 which were used in patients included in this study are listed in Supplemental Table 1 (adapted 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: (i) individual drugs administered, (ii) number of likely effective drugs used, and (iii) 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 being used at any time during treatment then the patient was considered 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 cells.

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, N.C.). For the individual patient data meta-analysis we used random effects multivariable logistic regression (random intercept and random slope) with penalized quasi-likelihood in order to evaluate the impact of drug-exposure on treatment outcomes (using PROC GLIMMIX in SAS) (21), (22), (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 analyzed. 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 to (i) treatment failure, relapse or death - for the analysis of individual drugs and number of drugs; and to (ii) failure or relapse - for the analysis of duration of treatment. Cases 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), (25), (26), (27), (28), (29), (30), (31), (32), (33), (34), (35), (36), (37), (38), (39), (40), (41), (42), (43), (44), (45), (46), (47), (48), (49), (50), (51), (52) (53), (54), (55) (Supplemental Table 2). Five centres did not have information about DST results to 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. Twenty-two 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 cases (6%) had XDR-TB.

The 6724 MDR-TB subjects had a mean age of 39.5 years (SD:13.5), 69% were male, 70% had been previously treated 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%). Less 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. Over 90% of XDR-TB patients had strains resistant to 6 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 (Figure 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, and more than 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 (Supplemental Table 1). Fluoroquinolones were used less often if resistance to them was detected (73–76% versus 91–92% if susceptible). Capreomycin was given more often than amikacin/kanamycin to patients with MDR-TB+INJr (56% versus 22% respectively) and XDR-TB (40% versus 33%). Almost 95% of patients in each sub-group received at least one Group 4 drug, usually ethionamide or prothionamide. Cycloserine/terizidone were given more often when MDR-TB patients had strains with additional resistance (84–89% versus 58% respectively), as was *p*-aminosalycilic acid (PAS; 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%). Six percent of all patients had had adjunctive lung resection surgery; this was most frequent in patients with MDR-TB+FQr (Supplemental Table 1).

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/kanamycin (over streptomycin) and ethionamide/prothionamide were significantly associated with treatment success. In the "MDR-TB only" patient group, the use of amikacin/kanamycin, capreomycin, ofloxacin, ethionamide/prothionamide, 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 were those on a regimen without a fluoroquinolone or which contained only first-line drugs (Supplemental Table 3). MDR-TB+INJr patients treated with a capreomycin-containing regimen fared worse than those who received kanamycin alone.

Treatment correlates with outcomes - number of drugs and duration

XDR-TB patients who in the intensive phase received 6 or more drugs likely to be effective, and "MDR-TB only" patients who received 4 drugs, had a higher likelihood of treatment success than patients receiving fewer drugs (Table 6). In the continuation phase, use of 4 drugs for XDR-TB patients and 3 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 lasting 6.6 to 9.0 months was associated with the maximal odds of treatment success (statistically significant) compared to 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 a fluoroquinolone, and then to both (XDR-TB). This effect is attributable to the gradual loss of effectiveness to the two classes of medications which 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), (9), (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/prothionamide, and cycloserine/terizidone or PAS. 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 classes of these drugs, 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 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 therefore less frequent (59). However, it could also be explained by previous exposure 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. 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 which 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 previously treated 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 in the world 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).

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 (Supplemental Table 2), located in many countries and in all WHO regions - enhancing the generalizability of findings. Detailed data, which were standardized 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

patients' characteristics. We had the opportunity to examine treatment correlates with outcomes that would not be possible with single centre reports.

Nevertheless this study does suffer from a number of important limitations. While attempts were made to standardize 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 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 randomized 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 individualized 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 DST 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).

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. Randomized controlled trials are needed to optimize 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 of 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 which 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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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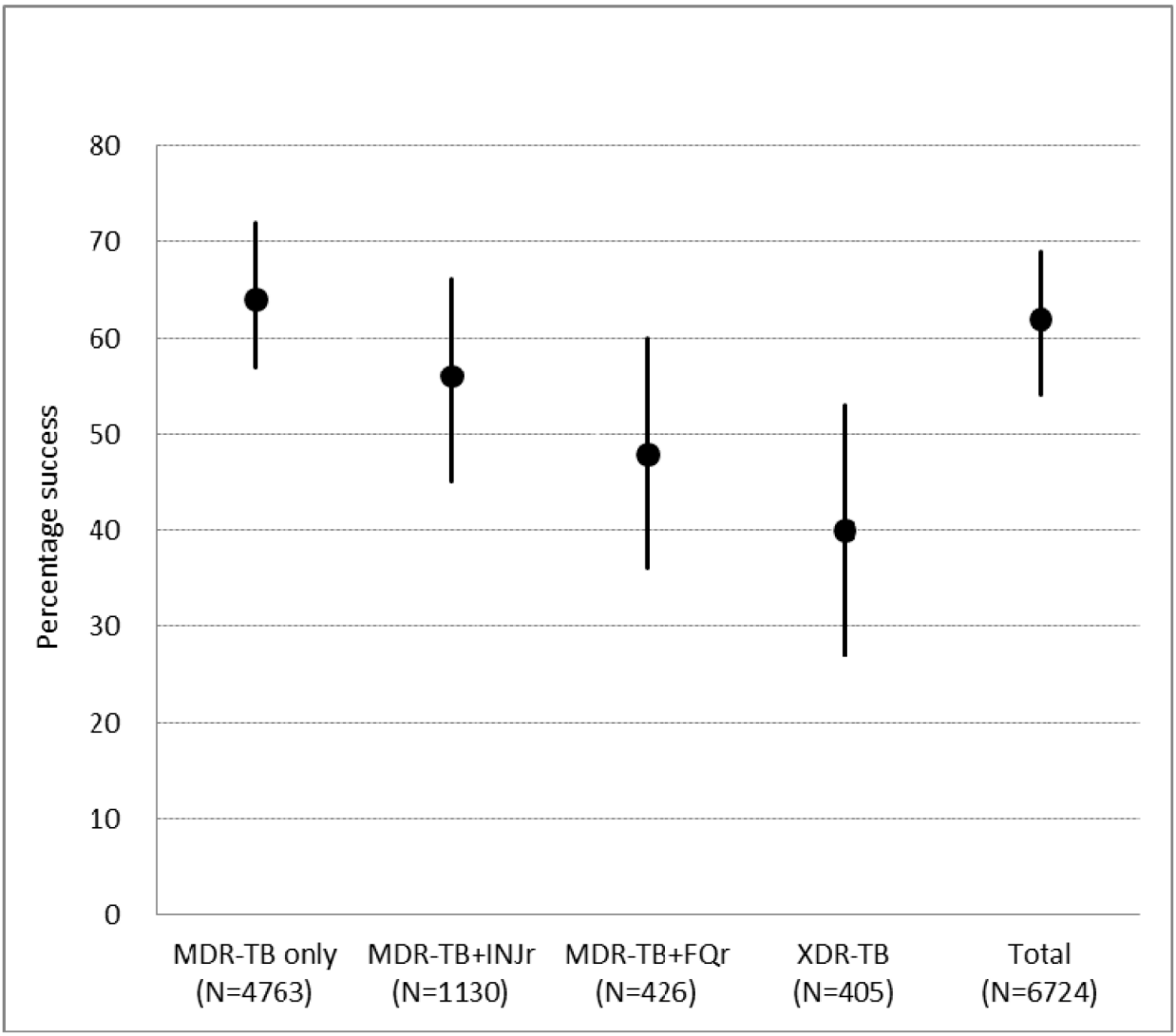

Figure 1. Treatment success among different MDR-TB patient groups
circles = point estimates; lines = 95% confidence interval

Table 1

Characteristics of MDR-TB patients with different resistance patterns of *M. tuberculosis*[*]

	MDR-TB, susceptible to FQ & INJ ("MDR-TB only")	MDR-TB+INJr	MDR-TB+FQr	XDR-TB	Total MDR-TB cases
Number of studies (N)	26	22	18	17	26
Number of cases	4763	1130	426	405	6724
Demographic characteristics					
Mean age in years (SD)	39.2 (13.5)	39.9 (13.3)	41.6 (14.3)	40.6 (13.8)	39.5 (13.5)
Male sex (%)	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 x-ray (%)	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 (%)	7%	16%	17%	27%	10%
Had a serious adverse event during therapy (%)	29%	47%	33%	43%	32%

[*] values shown in this table were computed using simple pooling across all studies. Percentages were calculated on patients in each group with information available

MDR-TB = multidrug-resistant TB; resistance to at least isoniazid ***and*** rifampicin

XDR-TB = extensively drug-resistant TB; MDR-TB plus resistance to any fluoroquinolone ***and*** any second-line injectable drug (amikacin/kanamycin and/or capreomycin)

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)

MDR-TB+INJr= MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones

MDR-TB, susceptible to FQ & INJ = MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested)

N: Number of cases

SD = standard deviation

Extensive disease defined as sputum-smear positive, or cavities on chest x-ray if information about sputum-smear was missing.

Previous TB treatment defined as treatment with any TB drug for one month or more. Previous treatment could be with first-line drugs or with two or more second-line drugs for MDR. In some patients information was only available that they were previously treated for TB but not whether this was with first or second-line drugs.

Table 2

Resistance to anti-tuberculosis drugs° by MDR-TB patient group

	MDR-TB, susceptible to FQ & INJ ("MDR-TB only") (N=4763) N (%)#	MDR-TB +INJr (N=1130) N (%)#	MDR-TB +FQr (N=426) N (%)#	XDR-TB (N=405) N (%)#	Total MDR-TB cases (N=6724) N (%)#
Resistance to:					
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%)
Resistant to amikacin/kanamycin and capreomycin	0 (-)	311 (33%)	0 (-)	82 (30%)	393 (13%)
Resistance to amikacin/kanamycin and capreomycin and streptomycin	0 (-)	295 (31%)	0 (-)	68 (25%)	363 (12%)
Group 4 drugs:					
Ethionamide/prothionamide	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 (PAS)	391 (14%)	281 (31%)	125 (31%)	127 (43%)	924 (21%)
Mean number of TB drugs tested (SD) **	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 (0%)	0 (0%)	2259 (34%)
3	947 (20%)	15 (1%)	19 (4%)	0 (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%)

	MDR-TB, susceptible to FQ & INJ ("MDR-TB only") (N=4763) N (%)#	MDR-TB +INJr (N=1130) N (%)#	MDR-TB +FQr (N=426) N (%)#	XDR-TB (N=405) N (%)#	Total MDR-TB cases (N=6724) N (%)#
8	9 (0.2%)	128 (11%)	25 (6%)	75 (19%)	237 (4%)
9	0 (0%)	37% (3%)	8 (2%)	46 (11%)	91 (1%)
10+	0 (0%)	2 (0.2%)	0 (0%)	35 (9%)	37 (0.3%)

° Drug-susceptibility test (DST) results for Group 5 drugs were available from very few centres and were not analyzed.

Number and percentage (%) of cases whose isolate was tested to that specific drug. All cases were tested for susceptibility to at least one fluoroquinolone 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 fluoroquinolones - results of these tests not shown. By definition, two patient groups were susceptible to FQ – hence 0 (-) marked in these columns

* Resistance to amikacin or kanamycin combined. Most centres tested for susceptibility to only one of these two drugs and considered them cross-resistant.

** Include tests to isoniazid and rifampin, as well as to fluoroquinolones and second-line injectable drugs - done in all cases

*** In addition to isoniazid and rifampin to which all patients were resistant being MDR-TB.

MDR-TB = resistance to at least isoniazid ***and*** rifampicin

XDR-TB = MDR-TB plus resistance to any fluoroquinolone ***and*** any second-line injectable drug (amikacin/kanamycin and/or capreomycin)

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)

MDR-TB+INJr = MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones

MDR-TB, susceptible to FQ & INJ = MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested)

N: Number of cases

Table 3

Treatment outcomes by MDR-TB patient group

Pooled treatment outcomes*	**MDR-TB, susceptible to FQ & INJ ("MDR-TB only") (N=4763) % (95%CI)**	**MDR-TB +INJr (N=1130) % (95%CI)**	**MDR-TB +FQr (N=426) % (95%CI)**	**XDR-TB (N=405) % (95%CI)**	**Total (N=6724) % (95%CI)**
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)

* From study level meta-analysis; column percentages do not total to 100%. See Methods and Laserson et al (2005) for treatment outcome definitions.

MDR-TB = resistance to at least isoniazid ***and*** rifampicin

XDR-TB = MDR-TB plus resistance to any fluoroquinolone ***and*** any second-line injectable drug (amikacin/kanamycin and/or capreomycin)

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)

MDR-TB+INJr = MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones

MDR-TB, susceptible to FQ & INJ = MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested)

N: Number of cases

CI = confidence intervals

Table 4

Association of treatment success with patient characteristics and MDR-TB patient group

Characteristics	Adjusted odds of treatment success vs treatment failure/relapse/death		
	N	aOR	(95%CI)
Male sex (vs female)*	4653	1.0	(0.9, 1.1)
Older age (per 10 year increment)*	6724	**0.8**	**(0.8, 0.9)**
HIV infected (vs not HIV infected)*	615	**0.3**	**(0.2, 0.4)**
Extensive disease (vs not)*	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 groups: †			
MDR, susceptible to FQ & INJ (“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 (vs not) †	373	1.5	(0.9, 2.6)
Experienced a serious adverse event (vs not) †	1511	1.0	(0.8, 1.2)

*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

N: Number of cases

aOR (adjusted odds ratios): odds ratios of treatment success (cure and completion) versus treatment failure/relapse/death. See Methods and Laserson et al (2005) for treatment outcome definitions.

CI = confidence intervals

MDR-TB = resistance to at least isoniazid ***and*** rifampicin

XDR-TB = MDR-TB plus resistance to any fluoroquinolone ***and*** any second-line injectable drug (amikacin/kanamycin and/or capreomycin)

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)

MDR-TB+INJr = MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones

MDR-TB, susceptible to FQ & INJ = MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested)

Table 5

Association of treatment success with individual drugs used in treatment by MDR-TB patient group

	MDR-TB susceptible to FQ & INJ ("MDR-TB only")			MDR-TB+INJr			MDR-TB+FQr			XDR-TB		
	N	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*	*N*	*aOR*	*(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: *(patients receiving 2 or more injectable drugs excluded from this analysis)*												
Amikacin or Kanamycin	2250			153			135			85		
vs 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)
vs 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)
vs 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		
vs no injectable drug		**2.2**	**(1.1, 4.2)**		0.9	(0.2, 4.1)		-	-		2.5	(0.9, 7.0)
vs Streptomycin		1.4	(0.6, 3.3)		0.8	(0.2, 3.9)		-	-		1.4	(0.1, 14)
Fluoroquinolones: *(patients receiving 2 or more fluoroquinolones excluded from this analysis. Insufficient number of patients received later- generation fluoroquinolones within the MDR-TB patient groups with additional resistance – so not analysed)*												
Ofloxacin	2956			787			197			227		
vs 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)
vs 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 prothionamide	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 (PAS)	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 (*Insufficient number of patients received specific Group 5 drugs within the MDR-TB patient groups with additional resistance so outcomes by individual Group 5 drugs not analysed)*												
Any one Group 5 drug vs 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 vs one Group 5	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 = resistance to at least isoniazid ***and*** rifampicin

XDR-TB = MDR-TB plus resistance to any fluoroquinolone ***and*** any second-line injectable drug (amikacin/kanamycin and/or capreomycin)

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)

MDR-TB+INJr = MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones

MDR-TB, susceptible to FQ & INJ = MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested)

N = number of cases that received the drug in question and were included in the specific analysis.

aOR (adjusted odds ratios): 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 more than 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 Laserson et al (2005) for treatment outcome definitions.

CI = confidence intervals

Later-generation fluoroquinolone = gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin

Group 5 drugs included amoxicillin/clavulanate, macrolides (azithromycin, clarithromycin, roxithromycin), clofazimine, thiacetazone, imipenem, linezolid, high-dose isoniazid and thioridazine.

Table 6

Association of treatment success with the number of effective drugs used in treatment by MDR-TB patient group

Table 6a: Number of drugs likely to be effective that were used during the intensive phase												
Number of drugs	**MDR-TB, susceptible to FQ & INJ ("MDR-TB only")**			**MDR-TB+INJr**			**MDR-TB+FQr**			**XDR**		
	N	***aOR***	***(95%CI)***	***N***	***aOR***	***(95%CI)***	***N***	***aOR***	***(95%CI)***	***N***	***aOR***	***(95%CI)***
0 – 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			47		
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)**

Table 6b: Number of drugs likely to be effective that were used during the continuation phase												
Number of drugs	**MDR-TB, susceptible to FQ & INJ ("MDR-TB only")**			**MDR-TB+INJr**			**MDR-TB+FQr**			**XDR**		
	N	***aOR***	***(95%CI)***	***N***	***aOR***	***(95%CI)***	***N***	***aOR***	***(95%CI)***	***N***	***aOR***	***(95%CI)***
0 – 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)

N: Number of cases

aOR (adjusted odds ratios): 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 more than 1 month with two or more second line drugs), and extent of disease. See Methods and Laserson et al (2005) for treatment outcome definitions

CI = confidence intervals

Intensive phase: is the initial part of a course of treatment during which an injectable drug is given. Continuation phase: is 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.

MDR-TB = resistance to at least isoniazid ***and*** rifampicin

XDR-TB = MDR-TB plus resistance to any fluoroquinolone ***and*** any second-line injectable drug (amikacin/kanamycin and/or capreomycin)

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)

MDR-TB+INJr = MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones

MDR-TB, susceptible to FQ & INJ = MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested)

Table 7

Association between duration of treatment and treatment success by MDR-TB patient group

7a. Duration of intensive phase

Duration of intensive phase (months)	MDR-TB, susceptible to FQ & INJ ("MDR-TB only")			MDR-TB+INJr			MDR-TB+FQr			XDR-TB		
	N	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*
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)

7b. Total duration of treatment

Total duration of treatment (months)	MDR-TB, susceptible to FQ & INJ ("MDR-TB only")			MDR-TB+INJr			MDR-TB+FQr			XDR-TB		
	N	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*	*N*	*aOR*	*(95%CI)*
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 = resistance to at least isoniazid ***and*** rifampicin

XDR-TB = MDR-TB plus resistance to any fluoroquinolone ***and*** any second-line injectable drug (amikacin/kanamycin and/or capreomycin)

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)

MDR-TB+INJr = MDR-TB plus resistance to amikacin/kanamycin and/or capreomycin, but susceptible to fluoroquinolones

MDR-TB, susceptible to FQ & INJ = MDR-TB, but susceptible to fluoroquinolones, amikacin/kanamycin and capreomycin (at least one second-line injectable drug tested)

N: Number of cases

aOR (adjusted odds ratios): odds ratios of treatment success versus treatment failure or relapse adjusted for age, sex, HIV infection, previous TB treatment, previous MDR treatment (treatment for more than 1 month with two or more second line drugs), and extent of disease. See Methods and Laserson et al (2005) for treatment outcome definitions

CI = confidence intervals

Intensive phase: is the initial part of a course of treatment during which an injectable drug is given. Continuation phase: is the period immediately following the initial phase when no injectable drug is given.