An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis

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There are many recent published studies, but these provide only very weak evidence on how to improve MDR-TB treatment http://ow.ly/zQa1308SSOi

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ABSTRACT This systematic review aimed to update the current evidence for multidrug-resistant tuberculosis (MDR-TB) treatment.

We searched for studies that reported treatment information and clinical characteristics for at least 25 patients with microbiologically confirmed pulmonary MDR-TB and either end of treatment outcomes, 6-month culture conversion or severe adverse events (SAEs). We assessed the association of these outcomes with patients' characteristics or treatment parameters. We identified 74 studies, including 17 494 participants.

The pooled treatment success was 26% in extensively drug-resistant TB (XDR-TB) patients and 60% in MDR-TB patients. Treatment parameters such as number or duration and individual drugs were not associated with improved 6-month sputum culture conversion or end of treatment outcomes. However, MDR-TB patients that received individualised regimens had higher success than patients who received standardised regimens (64% *versus* 52%; p<0.0.01). When reports from 20 cohorts were pooled, proportions of SAE ranged from 0.5% attributed to ethambutol to 12.2% attributed to para-aminosalicylic acid. The lack of significant associations of treatment outcomes with specific drugs or regimens may reflect the limitations of pooling the data rather than a true lack of differences in efficacy of regimens or individual drugs.

This analysis highlights the need for stronger evidence for treatment of MDR-TB from better-designed and reported studies.

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Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to at least isoniazid (INH) and rifampin (RIF), and extensively drug-resistant TB (XDR-TB), defined as resistance to INH and RIF plus at least one fluoroquinolone and one second-line injectable drug, have become major public health threats [1]. The World Health Organization (WHO) has estimated that, in 2015, approximately 580 000 people developed MDR-TB, of whom 55 000 had XDR-TB [2].

Treatment for MDR-TB or XDR-TB requires lengthy use of second-line TB drugs, although the regimens used vary widely due to differences in opinions as well as the resources available [3, 4] To date, there are few published phase 3 randomised clinical trials (RCTs) for MDR-TB treatment. Hence, systematic reviews [5–7] and individual patient data (IPD) meta-analyses [8] have provided the majority of evidence for MDR-TB/XDR-TB treatment [9]. However, this meta-analysis only included studies published up until 2008 [8], and since then a large number of studies with new drugs and new regimens for MDR-TB/XDR-TB have been published. We therefore performed this systematic review to update the evidence for MDR-TB treatment to inform the WHO Guideline Development Group.

Methods

Literature search and study selection

The PICO (Patients, Intervention, Comparator and Outcomes) questions were developed by a WHO Guideline Development Group to answer specific questions regarding MDR-TB treatment (see supplementary material for the PICO questions). The main focus of this review was the efficacy and safety of the drugs available for treatment of MDR-TB patients. The following groups of drugs were analysed: first-line drugs (pyrazinamide and ethambutol), injectable drugs (streptomycin, kanamycin, amikacin and capreomycin), fluoroquinolones (ofloxacin, levofloxacin and moxifloxacin), add-on agents (ethionamide/prothionamide, cycloserine, para-aminosalicylic acid (PAS) and high-dose isoniazid) and bedaquiline. Four independent systematic reviews [10–13] have been conducted recently for the group 5 drugs (renamed as "add-on agents" by WHO), so we did not include these drugs specifically in our search. However, if a study reported the use of any group 5 drugs, we abstracted the information.

We searched MEDLINE (through OVID), EMBASE (through OVID) and The Cochrane Library. The search strategy used a combination of Medical Subject Heading terms and free-text words in titles, abstracts and key words. Terms related to MDR- or XDR-TB, drugs and treatment outcomes were included (supplementary material). Because this is an update from previous reviews that included studies published up to December 2008, our search was limited to the period from January 2009 to August 2015.

Titles, abstracts and full texts were screened by two reviewers (M.L. Bastos and Z. Lan), with consensus in each stage. A third reviewer (D. Menzies) was consulted to resolve disagreements. We included studies published in English, French, Chinese, Portuguese and Spanish. All studies that met the following inclusion criteria were selected: 1) MDR-TB confirmed by phenotypic tests (GeneXpert® alone for diagnosis of MDR-TB was not considered adequate unless confirmed by phenotypic tests), 2) pulmonary TB, 3) cohorts or RCTs with a minimum of 25 patients treated, 4) a clear description of the regimen and the drugs received, and 5) at least one of the following reported: end of treatment outcomes; 6-month sputum culture conversion; treatment adverse events. Studies that evaluated short regimens (<18 months) were excluded, as these have been reviewed elsewhere [14]. For studies that reported patients with extra-pulmonary disease, due to the difficulty of microbiological confirmation for the initial diagnosis and the even greater difficulty of confirmation of cure at the end of treatment, we excluded studies in which more than 10% of patients had extra-pulmonary disease, and did not report results stratified by disease site.

Data abstraction

We recorded information about age, sex, HIV (and use of antiretroviral treatment), acid-fast bacillus smear results, chest radiography cavitation, prior TB treatment (with first-line drugs or second-line drugs), drug susceptibility test results, number of patients that received each drug, duration of treatment, and whether the regimen was standardised or individualised. Outcomes abstracted included end of treatment outcomes, 6-month sputum culture conversion, and severe adverse events defined as grade 3–4 events, or defined operationally as events resulting in permanent discontinuation of a drug.

Quality assessment

There are no validated criteria for evaluating quality in MDR-TB studies, so we developed a checklist based on the presence of 12 indicators, grouped into four major categories:

1) Diagnostic information (three items): i) reported methods of confirmation of TB and of MDR-TB; ii) reported results of drug susceptibility testing for ethambutol or pyrazinamide; and iii) reported results of drug susceptibility testing for fluoroquinolones or second-line injectable.

2) Treatment regimen information (five items): i) duration of intensive phase; ii) number of drugs used in intensive phase; iii) duration of continuous phase; iv) number of drugs used in continuous phase; and v) dosage of drugs used.

3) Adverse event information (two items): i) provided a definition of adverse event (*e.g.* graded, classified by severity); and ii) the drug considered related to the adverse event was identified.

4) End of treatment information (two items): i) if the end of treatment outcomes were defined using Laserson *et al.* [15] or WHO [1] definitions (2013); and ii) if default rate was ⩽8% (this threshold for quality was calculated by subtracting the pooled estimation of fail/relapse and death (17%) of all cohorts included in the review, from the WHO predefined target of a total of 25% non-success for MDR patients) [16].

The score was an unweighted sum of the 12 indicators.

Data synthesis and statistical analysis

For end of treatment outcomes, we compared success (defined as cured or treatment completed) to 1) failure or relapse or 2) failure or relapse or death. Analysis was stratified according to resistance pattern (MDR or XDR) and whether the regimen was individualised or standardised. In additional analyses, we examined the relationship of the pooled success and the prevalence of additional resistance to the second-line injectable or fluoroquinolones (*i.e.* pre-XDR-TB patients) among the MDR patients. We examined the relationship between each effectiveness end-point (end of treatment outcome and 6-month sputum culture conversion) and the number of patients receiving each specific drug, the average number of drugs used and duration of treatment, as well as the average value, for each cohort, of the major clinical and demographic characteristics of the patients. If HIV or age were missing, values were estimated using information from other included studies from the same country, or if this was not available, from data published by the World Bank [17] or WHO [18]. Variables were categorised according to the distribution observed (median, terciles or quartiles).

The occurrence of severe adverse events was pooled across studies that reported the following: the drug related to the event; events classified as grade 3 or 4 severity; or permanent discontinuation of a drug related to the event.

All statistical analyses were performed using SAS (version 9.2 Institute, Cary, NC, USA). Linear mixed models were used to pool the proportion with events and generalised linear mixed model for pooling adverse events.

Results

Description of studies

As shown in figure 1, 2336 titles were identified and, after eliminating duplicates and non-relevant publications based on a review of titles and abstracts, 250 were selected for full text review. In total, 176 studies were excluded, including 24 classified as "MDR-TB not confirmed". These 24 studies reported cohorts in which outcomes of patients with MDR-TB were reported together with outcomes of patients with fully susceptible TB, or poly-drug resistant, or non-confirmed MDR-TB ("suspicious of drug resistant TB"). None was excluded due to reliance only on GenXpert results.

Of the 74 studies that met the review inclusion criteria [19–92], seven [27, 34, 36, 51, 60, 66, 68] reported more than one cohort, yielding a total of 84 cohorts with 17 494 patients with MDR- or XDR-TB. Of these, 64 studies reported microbiological outcomes at the end of treatment and/or 6-month sputum culture conversion, and 44 reported adverse events. Of the latter group, only 19 studies reported events that were classified as grade 3 or 4, or required permanent discontinuation of the drug and identified the drug considered related.

Of the 74 studies, seven reported results in patients with XDR-TB only. 14 (13 cohorts) studies included patients with MDR-TB and XDR-TB, and treatment outcomes (one cohort reported 6-month sputum culture conversion and 12 cohorts reported end of treatment) were reported separately for these two groups of patients. Seven studies reported only MDR-TB patients, and 46 studies (57 cohorts) reported MDR-TB patients but did not provide information regarding drug susceptibility testing to fluoroquinolones and second-line injectable. Hence, some patients in these studies may have had XDR-TB. As seen in table 1, of the 17 494 patients, 4623 (66% of those with information) had a history of prior treatment with first-line drugs, 5088 (55% with chest radiography information) had cavitation on chest radiograph and 6057 (69% with acid-fast bacilli (AFB) results) were AFB sputum smear positive. Only 3111 (19% of tested) had HIV co-infection, of whom 1311 (42%) were on anti-retroviral treatment. More detailed study design, demographic, clinical treatment and outcome information are summarised in supplementary tables S1–S7.

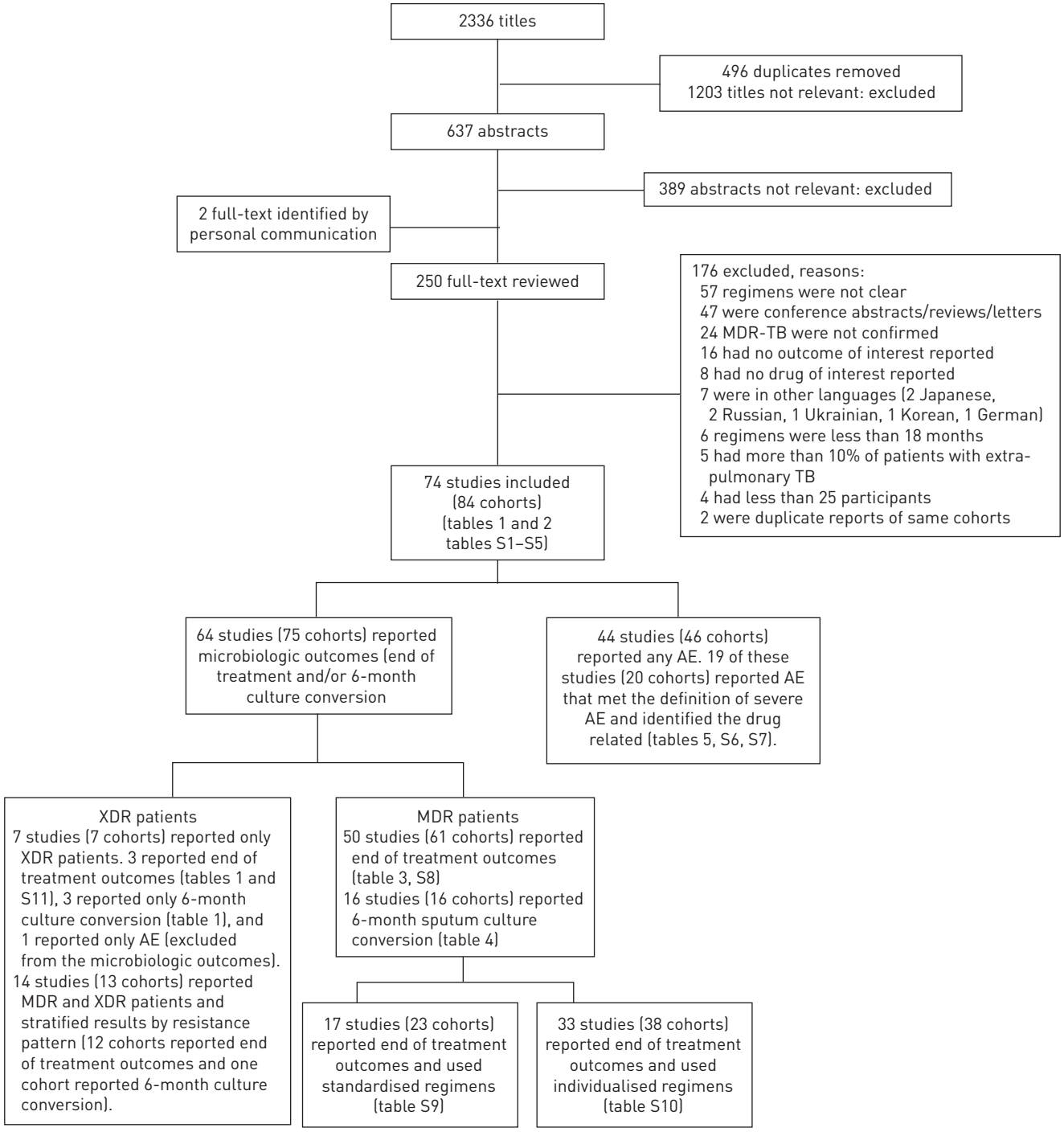

FIGURE 1 PRISMA diagram of study selections in the review (and guide to applicable tables). TB: tuberculosis; MDR: multidrug-resistant; XDR: extensively drug-resistant; AE: adverse event.

Study quality

All studies were assessed for quality based on the reporting of essential diagnostics, treatment and outcome information. As seen in table 2, only half to two-thirds of studies reported each of the three diagnostic information items considered essential and, only one-third of studies reported all three items adequately. Only 20–39% of studies reported each of the five treatment information items, and only two studies (3%) reported all five items adequately. Of the two items considered essential for adverse events, only half of the studies who reported any adverse events provided both. On the other hand, 51 of 54 studies reported end of treatment outcomes, defined as recommended by WHO [1] or Laserson *et al.* [15]. Only 25% of studies achieved a lost to follow-up rate less than 8%. Supplementary table S2 provides details about these criteria.

Treatment outcomes and correlates

As shown in table 1, the pooled treatment success was 26% (95% CI 23–30%) in XDR-TB patients, compared to 60% in all cohorts of MDR-TB patients (with or without "pre-XDR"). In the studies providing this information, studies with a higher proportion of pre-XDR-TB patients reported similar outcomes to all other studies of MDR-TB patients (supplementary table S8), so these results were pooled together. Because the outcomes for XDR-TB patients were substantially worse than in MDR-TB patients, the XDR-TB patients were analysed separately from MDR-TB patients in the end of treatment outcome and in 6-month sputum culture conversion.

The pooled treatment success for MDR-TB patients that received individualised regimens was significantly higher when compared with patients who received standardised regimens (64% *versus* 52%; table 1). As shown in table 3, in 61 cohorts of MDR-TB patients, the end of treatment outcomes were not associated with any patients' characteristics or treatment parameters, including duration, number of drugs or individual drugs. When the same analysis was stratified in cohorts of MDR-TB patients who received only standardised or only individualised regimens, similar results were found (supplementary tables S9 and S10). Similar results were found when we analysed failure separately from relapse (data not shown).

No treatment or patient characteristics examined were associated with end of treatment outcomes in the 15 cohorts of XDR-TB patients (supplementary table S11).

The pooled estimation of the 6-month sputum culture conversion was 69% in MDR-TB patients and 19% in XDR-TB patients (table 1). As shown in table 4, in 16 cohorts of MDR patients, sputum conversion was not associated with any of the reported patients' characteristics or treatment parameters. We could not assess the relationship between treatment regimens, clinical characteristics and 6-month sputum culture conversion for XDR-TB patients due to unstable results when we pooled the data.

Only 19 studies (20 cohorts) met the criteria for pooling severe adverse event data, and 86% of the patients included in these cohorts had received individualised regimens (supplementary table S7). All 20

TABLE 1 Summary of available clinical treatment and outcome information for multidrug-resistant and extensively drug-resistant tuberculosis (MDR- and XDR-TB) patients

Characteristics of study participants	MDR-TB patients (with or without resistance to FQN or SLI, not XDR)			XDR-TB[1] patients	All patients
	Standardised treatment	Individualised treatment	Total MDR-TB patients		
Total number of studies (cohorts)	22 (28)	45 (49)	67 (77)	7 (7)	74 (84)
Total number of participants	5954	10543	16497	997	17494
Age median years	34	38	38	35	36
Clinical characteristics[2]					
History of prior treatment with FLD	1714/1827	2859/5030	4573/6857	50/107	4623/6964
History of prior treatment with SLD	25/613	1192/5452	1217/6065	486/706	1703/6771
Patients with cavitation on CXR	324/508	4649/8504	4973/9012	115/249	5088/9261
Patients with HIV co-infection	1767/5427	815/9874	2582/15301	529/971	3111/16272
Patients with HIV receiving ART	483/1767	476/815	959/2582	344/529	1303/3111
Positive AFB smears	1798/2665	3995/5674	5793/8339	264/504	6057/8843
Drugs received					
Pyrazinamide	5669	4948	10617	855	11472
Ethambutol	1908	2709	4617	678	5295
Amikacin/kanamycin	4763	4219	8982	56	9038
Capreomycin	68	2352	2420	823	3243
Ofloxacin/ciprofloxacin	4587	5023	9610	139	9749
Moxifloxacin/levofloxacin	969	3686	4655	150	4805
Thiamide	5927	5970	11897	731	12628
Cycloserine/terizidone	2462	5044	7506	720	8226
PAS	214	4947	5161	849	6010
6-month sputum culture conversion					
Number of studies (cohorts)	6 (6)	10 (10)	16 (16)[3]	4 (4)[3]	19 (19)[3]
Number of participants	653	2563	3216	505	3721
With conversion					
Number	470	1515	1985	99	2084
% (95% CI)[3,4]	75 (60–90)	66 (51–79)	69 (58–80)	19 (14–23)	62 (48–76)

Continued

TABLE 1 Continued

Characteristics of study participants	MDR-TB patients (with or without resistance to FQN or SLI, not XDR)			XDR-TB[1] patients	All patients
	Standardised treatment	Individualised treatment	Total MDR-TB patients		
EOT outcomes					
Number of studies (cohorts)	17 (23)	33 (38)	50 (61)	15 (15)[1]	53 (64)[1]
Number of participants	5059	9044	14 103	730	14 833
Success[5]					
Number	2631	5797	8428	193	8621
% (95%CI)[8]	52% (50–54)	64% (63–65)	60% (58–61)	26% (23–30)	58% (57–59)
Fail[6]					
Number	519[7]	992	1511	273[9]	1784
% (95%CI)[8]	10% (9–11)	12% (11–13)	11% (10–12)	42% (40–44)	13% (12–14)
Fail/relapse[6]					
Number	519	1037	1556	273[9]	1829
% (95%CI)[8]	10% (9–11)	13% (12–13)	12% (11–12)	42% (40–44)	13% (12–14)
Death[6]					
Number	839	646	1485	146	1631
% (95%CI)[8]	17% (16–18)	8% (7–9)	11% (11–12)	21% (18–25)	12% (11–13)
Lost to follow-up					
Number	1045	1307	2352	98	2450
% (95%CI)[8]	21% (19–22)	16% (15–16)	18% (17–18)	14% (11–18)	17% (17–18)
All non-success[10]					
Number	2428	3247	5675	537	6212
% (95%CI)[8]	48% (47–50)	36% (35–37)	39% (40–41)	74% (70–77)	42% (41–43)

FQN: fluoroquinolone; SLI: second-line injectable; FLD: first-line drug; SLD: second-line drug; CXR: chest radiograph; ART: anti-retroviral treatment; AFB: acid-fast bacilli; PAS: para-aminosalicylic acid; EOT: end of treatment. [1]: seven studies (seven cohorts) reported only XDR-TB patients, of which three reported EOT outcomes and three reported 6 month sputum conversion. Another 12 studies reported EOT outcomes stratified by resistance pattern (XDR were separated from MDR). These 12 studies did not stratify the clinical or demographic variables according to resistance pattern, so, for the description of clinical and demographic information of the XDR-TB patients, we used the information from the seven studies that reported only XDR-TB patients. For the pooled EOT analysis, we combined the results from the three cohorts of only XDR-TB patients and the 12 cohorts of XDR-TB patients from the studies that reported stratified results. [2]: for clinical characteristics variables we added the denominator, because not all studies reported the clinical variables. The report of these clinical variables was not a criterion for inclusion in the review. [3]: one study stratified results of 6-month culture conversion by resistance pattern. Thus, this study is shown in both the XDR column and MDR total column. [4]: pooled using Proc Glimmix in SAS – random effects meta-analysis. [5]: success was defined as cure or treatment complete. [6]: four studies were excluded from the analysis of fail/relapse: two reported fail and death together; one reported fail/death/loss to follow-up together; and the other reported fail/death/loss to follow-up/relapse together. The last two were also excluded from loss to follow-up analysis. One XDR study that reported fail and death together was excluded from the analysis of fail/relapse and death. [7]: no studies that reported standardised regimens reported fail separated from relapse. [8]: pooled using Proc Glimmix in SAS – fixed effects meta-analysis. [9]: no studies that reported XDR reported fail separated from relapse. [10]: all non-success includes fail, relapse, death and loss to follow-up.

cohorts reported the number of patients that had adverse events and not the number of events, so the denominators used in adverse event analysis were the number of patients that received the specific drug.

As shown in table 5, the occurrence of severe adverse events ranged from 0.5% of 1325 patients receiving ethambutol to 12.2% of 1706 patients who received PAS. Fewer than 3% of patients receiving fluoroquinolones or pyrazinamide experienced an severe adverse event, compared to more than 5% of patients receiving second-line injectables or a thiamide (ethionamide or prothionamide). Detailed information on the reporting of adverse events is provided in supplementary tables S6 and S7.

Discussion

This review identified 74 studies, with 84 distinct cohorts, published since January 2009, that reported treatment regimens and outcomes in 17 494 MDR-TB and XDR-TB patients. These studies have reported adverse events, 6-month sputum culture conversion, and end of treatment outcomes. The pooled overall success of MDR patients was 60%: similar to previously reported studies [5–8] and well below the WHO target of 75% [16]. Treatment outcomes were substantially worse in patients with XDR-TB and in patients who received standardised regimens for MDR-TB.

However, despite the large number of studies and patients, no other treatment parameter, including number or duration of drugs and individual drugs, were associated with 6-month culture conversion, or end of treatment outcomes. This lack of association in many treatment parameters (use of any individual drugs,

TABLE 2 Quality of the studies included in the review

	Studies reporting	Quality scores		
	Number of studies	Maximum score possible	Median score	Studies[#] with the maximum score %
Diagnostic information (all studies)				
Methods of MDR confirmation reported	48	1		66
DST for EMB/PZA reported	36	1		49
DST for FQN/SLI reported	42	1		58
Total: for studies that reported diagnostic information	74	3	2	34
Treatment regimen information (all studies)				
Duration of intensive phase reported	29	1		39
Number of drugs used in intensive phase reported	26	1		35
Duration of continuation phase reported	27	1		36
Number of drugs used in continuation phase reported	20	1		27
Drug doses reported	15	1		20
Total: for studies that reported treatment Information	74	5	1	3
AEs				
Provided a definition for AE	28	1		65
Identified the drug related to AE	26	1		60
Total: for studies that reported adverse events	44	2	1	50
EOT outcomes				
Outcome met Laserson *et al.* [15] or WHO [1] definition	51	1		94
Loss to follow-up rate <8%[#,¶]	13	1	–	25
Total; for studies that reported EOT outcomes	54	2	1	22
Total score percentage[+]	74	100%	42%	0%

MDR: multidrug resistance; DST: drug susceptibility testing; EMB: ethambutol; PZA: pyrazinamide; FQN: fluoroquinolone; SLI: second-line injectable; EOT: end of treatment; AE: adverse event. [#]: two studies reported loss to follow-up together with other unsuccessful outcomes and were excluded from analysis of loss to follow-up. Note that they were not excluded from all the assessments of quality. [¶]: the threshold for quality based on rate of loss to follow-up of 8% was calculated by subtracting the pooled estimation of fail/relapse and death (17%) of all cohorts included in the review from the WHO predefined target of a total of 25% non-success for MDR patients. [+]: total score percentage is score for the study/maximum possible score for the study. The maximum possible score for studies was based on the outcomes reported: only reported 6-month culture conversion, 8; only reported EOT outcome, 10; only reported AE, 10; reported 6-month culture conversion and AE, 10; reported EOT outcome and AE, or all three outcomes, 12.

treatment length, number of drugs) and clinical characteristics (such as HIV co-infection) was also observed in three previous systematic reviews [5–7]. This may reflect the limitations and difficulties of pooling the data rather than a true lack of differences in efficacy of regimens or individual drugs. This limited pooling to simple characterisation, such as stratifying analyses at the median value for proportion receiving a certain drug. This crude characterisation resulted in misclassification of exposure for many patients treated with individualised regimens and reduced our chances of finding any effects, even if present.

This review highlights the need for more standardised reporting as well as evidence from well-designed randomised trials, or from meta-analysis of pooled individual patient data from multiple observational studies.

This review has a number of strengths, the most important being the identification of a large number of studies, published within the past 7 years, describing three important outcomes of MDR-TB treatment: 6-month sputum culture conversion, severe drug-related adverse events, and end of treatment outcomes. This comprehensive aggregate meta-analysis was used to update the WHO recommendation [93] of MDR-TB treatment. The treatment regimen should include four core second-line drugs: one from group A (fluoroquinolones), one from group B (second-line injectable agents) and two from group C (ethionamide/prothionamide, cycloserine/terizidone, linezolid, clofazimine), plus pyrazinamide. If there is clinical or *in vitro* evidence of resistance to these drugs, other add-on agents from group D2 (bedaquiline or delamanid) and group D3 (PAS, imipenem–cilastatin/meropenem, amoxicillin–clavulanate) can be added, preferably drugs from group D2 [93].

However, our study had a number of important limitations, the most important being that almost all included studies were observational, and the majority described results with individualised treatment regimens. Selection bias is an important limitation for these studies of individualised regimens, because sicker patients with more extensive disease or drug resistance may have been more likely to receive certain drugs such as later-generation fluoroquinolones. Additionally, the 23 cohorts describing standardised regimens used very different regimens (supplementary table S4), so we could not pool by different types of standardised regimens.

TABLE 3 Covariates associated with end of treatment (EOT) outcomes in the 61 cohorts of multidrug-resistant tuberculosis patients (extensively drug-resistant tuberculosis (XDR-TB) excluded)[1]

Variable	Success/success+fail+relapse				Success/success+fail+relapse+death			
	Cohorts	Events	Pooled success		Cohorts	Events	Pooled success	
			Estimate %	95% CI			Estimate %	95% CI
Any patients with HIV co-infection								
No	31	2439/3010	88	83–93	31	2439/3300	79	73–85
Yes	30	5989/6974	94	91–97	30	5989/8194	80	74–86
Number of drugs used in the initial intensive phase[2]								
<6 drugs	24	3358/4026	91	87–95	24	3358/4872	79	74–84
6 drugs	20	2821/3259	90	85–94	20	2821/3629	77	72–83
>6 drugs	5	204/278	84	70–99	5	204/301	72	54–93
Duration of intensive phase[3]								
4–5 months	3	1584/1987	80	70–91	3	1584/2657	59	51–68
6–7.4 months	11	1647/1848	94	92–97	11	1647/2081	81	77–85
⩾7.5 months	7	429/486	87	82–93	7	429/590	71	65–78
Age[4] (median)								
⩽37.6 years	30	4163/4903	92	88–96	30	4163/5949	80	74–86
>37.6 years	31	4265/5081	91	86–95	31	4265/5545	79	73–85
Patients who received pyrazinamide[5]								
<84%	26	4548/5247	89	85–95	26	4548/5731	79	73–86
⩾84%	28	3314/3396	92	88–96	28	3314/4969	79	71–85
Patients who received ethambutol[6]								
0%	20	2041/2351	89	83–95	20	2041/2625	79	71–87
0.1–49.9%	13	2603/3043	89	82–96	13	2603/3345	78	68–88
⩾50%	22	2158/2471	95	91–98	22	2158/2856	84	78–90
Used streptomycin for any of the patients[7]								
Yes	18	3355/3810	97	95–99	18	3355/4116	88	83–93
No	43	5073/6174	88	84–92	43	5073/7378	75	70–81
Patients who received amikacin/kanamycin[8]								
⩽71%	20	3378/3942	89	83–96	20	3378/4282	78	70–86
>71%	23	3336/3935	94	90–97	23	3336/4741	82	75–88
Used capreomycin for any of the patients[9]								
Yes	22	3960/4658	92	87–97	22	3960/5141	77	69–84
No	21	2754/3219	93	88–97	21	2754/3882	83	76–89
Patients who received ofloxacin/ciprofloxacin[10]								
⩽78.9%	22	3148/3644	92	88–96	22	3148/4025	82	76–87
>78.9%	24	4387/5202	91	85–96	24	4387/6210	78	71–84
Used levofloxacin for any of the patients[11]								
Yes	16	2641/3049	93	88–98	16	2641/3349	82	75–89
No	28	4590/5447	90	86–95	28	4590/6472	78	72–84
Used moxifloxacin for any of the patients[11]								
Yes	16	3303/3840	92	87–96	16	3303/4166	81	75–89
No	28	3928/4656	91	87–97	28	3928/5655	78	72–84
Used later-generation FQN for any of the patients[12]								
Yes	27	4270/4978	91	85–95	27	4270/5474	80	74–85
No	21	3397/4046	92	87–96	21	3397/4958	78	74–85

Continued

TABLE 3 Continued

Variable	Success/success+fail+relapse				Success/success+fail+relapse+death			
	Cohorts	Events	Pooled success		Cohorts	Events	Pooled success	
			Estimate %	95% CI			Estimate %	95% CI
Patients who received cycloserine/terizidone[13]								
0%	14	1969/2479	87	78–96	14	1969/2823	79	69–89
0.1–90.9%	16	2988/3324	94	90–98	16	2988/3623	84	76–91
⩾91%	23	1756/1961	93	89–96	25	1756/2293	78	71–86
Patients who received thiamide[14]								
0–71.9%	12	1575/1840	92	87–98	12	1575/1979	85	78–93
72.0–91.9%	14	3210/3764	88	80–96	14	3210/4109	76	67–86
⩾92%	30	3175/3737	93	89–96	30	3175/4723	78	72–85
Used PAS for any of the patients[15]								
Yes	27	4981/5744	93	89–96	27	4981/6276	81	75–87
No	28	2968/3595	90	85–95	28	2968/4521	78	71–85
Used high-dose isoniazid (no studies)[16]								
Used bedaquiline (only one study used)[17]								
Patients who received other add-on drugs (group 5)[18]								
0%	34	4482/5260	91	89–94	34	4482/6474	76	71–81
0.1–25%	10	1405/1501	96	93–100	10	1405/1578	93	85–100
>25%	13	2175/2672	85	75–95	13	2175/2589	76	68–84
Used linezolid for any of the patients?[19]								
Yes	7	582/636	97	91–100	7	582/678	89	79–98
No	50	7480/8797	91	88–94	50	7480/10 233	79	74–83
Used clofazimine for any of the patients?[20]								
Yes	8	431/511	96	88–100	8	431/546	85	70–99
No	49	7631/8922	91	89–94	49	7631/10 365	79	75–84

FQN: fluoroquinolone; PAS: para-aminosalicylic acid. [1]: of the 84 cohorts, 64 reported EOT outcomes (similar or equal to criteria of Laserson *et al.* [15]), three cohorts that only reported XDR-TB cases were excluded from the analysis. All identified XDR cases were excluded from EOT outcomes. [2]: information was missing in 12 cohorts, so they were excluded from the analysis. [3]: of the 61 cohorts, only 21 reported duration of intensive phase. [4]: median (based on all eligible cohorts for this analysis) was used to categorise the variable. [5]: seven cohorts had no clear information of how many participants used the drug, so they were excluded from the analysis. Median was used to categorise the variable. [6]: six cohorts had no clear information of how many participants used the drug, so they were excluded from the analysis. The strata were defined using three major clusters. [7]: one cohort had no clear information of how many participants used the drug, so they were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used". [8]: 18 cohorts had no clear information of what second line injectable was used, so they were excluded from the analysis. The strata were defined using two major clusters, using the median value. [9]: 18 cohorts had no clear information of what second line injectable was used, so they were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used". [10]: 15 cohorts had information missing: in 12 cohorts it was not clear what FQN was used (later or early generation), and in three cohorts it was not clear how many participants used ciprofloxacin or ofloxacin. All 15 cohorts were excluded from the analysis. The median was used to categorise the variable. [11]: 17 cohorts had information missing: in 12 cohorts it was not clear what FQN was used (later or early generation), in four cohorts it was not clear what later generation was used (moxifloxacin or levofloxacin) and in one cohort it was not clear how many participants used the drug. All 17 cohorts were excluded from the analysis. The strata were defined using two major clusters. [12]: 13 cohorts had information missing: in 12 cohorts it was not clear what FQN was used (later or early generation) and in one cohort it was not clear how many participants used the drug. All 13 cohorts were excluded from the analysis. The strata were defined using two major clusters. [13]: eight cohorts had no clear information about how many participants used the drug, so they were excluded from the analysis. Three major strata were used to categorise the variable. [14]: five cohorts had no clear information on how many participants used the drug, so they were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used". [15]: six cohorts had no clear information on how many participants used the drug, so they were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used". [16]: no studies reported the use of high-dose isoniazid.[17]: only one study reported the use of bedaquiline and reported EOT outcomes, so it was not pooled. [18]: four cohorts had no clear information on how many participants used any group 5 drug, so they were excluded from the analysis. Other add-on drugs: amoxicillin/clavulanate, clarithromycin, clofazimine, linezolide, thiacetazone. [19]: four cohorts had no clear information on how many participants used any group 5 drug. [20]: four cohorts had not no clear information on how many participants used any group 5 drug.

TABLE 4 Covariates associated with 6-month sputum culture conversion in the 16 cohorts of multidrug-resistant tuberculosis patients (extensively drug-resistant tuberculosis (XDR-TB) excluded)[1]

Variables	Cohorts	Events	Pooled	
		n/N	Estimate %	95% CI
Age[2] (median)				
⩽34 years	9	1445/2221	67	53–82
>34 years	7	540/995	72	57–88
Any patients with HIV co-infection				
No patients	6	292/443	77	61–92
Yes, some patients	10	1693/2773	65	51–79
Number of drugs used in the initial intensive phase[3]				
4–5	8	1278/1862	74	59–89
⩾6	5	303/527	73	54–92
Duration of intensive phase (no cohort reported less than 5 months so not analysed)[4]				
Patients who received pyrazinamide[5]				
<94%	7	1368/2362	55	42–67
⩾94%	7	527/721	72	67–86
Patients who received ethambutol[6]				
<32.6%	6	391/595	65	50–80
⩾32.6%	7	1438/2408	64	50–79
Streptomycin used for any of the patients[7]				
Yes	4	1261/2178	49	29–70
No	12	724/1038	75	65–84
Patients who received amikacin/kanamycin[8]				
⩽78.5%	5	1290/2211	56	40–71
>78.5%	6	371/578	67	54–80
Capreomycin used for any of the patients[9]				
Yes	6	1338/2331	50	40–60
No	5	323/458	75	66–85
Patients who received ofloxacin/ciprofloxacin[10]				
⩽74.1%	4	544/946	77	60–94
74.2–98.4%	4	985/1612	49	27–71
⩾98.5%	6	391/555	76	62–89
Levofloxacin used for any of the patients[11]				
Yes	5	1411/2361	58	41–75
No	8	577/808	69	57–82

Continued

TABLE 4 Continued

Variables	Cohorts	Events	Pooled	
		n/N	Estimate %	95% CI
Moxifloxacin used for any of the patients[11]				
Yes	5	1301/2263	49	35–63
No	8	577/808	74	66–83
Later-generation FQN used for any of the patients[12]				
Yes	8	1529/2558	54	48–81
No	6	391/555	76	61–91
Patients who received thiamide[13]				
⩽79.8%	3	380/750	60	38–82
79.9–99.9%	4	1005/1589	62	44–81
100%	7	510/738	71	59–83
Patients who received cycloserine[14]				
⩽39.3%	3	1221/1961	69	53–86
39.4–99.9%	5	204/469	52	37–68
100%	6	470/653	74	63–85
PAS used[15]				
Yes	7	1366/2366	54	42–66
No	7	529/717	74	68–86
High-dose isoniazid used (no studies)[16]				

FQN: fluoroquinolone; PAS: para-aminosalicylic acid. [1]: of 84 cohorts, only 16 reported 6 month culture conversion (10 individualised and six standardised). All identified XDR cases were excluded from this analysis. [2]: the median (based on all eligible cohorts for this analysis) was used to categorise the variable. [3]: three cohorts had missing information, so they were excluded from the analysis. [4]: nine cohorts had missing information, so they were excluded from the analysis. [5]: two cohorts had no clear information on how many participants used the drug, so they were excluded from the analysis. The median was used to categorise the variable. [6]: three cohorts had no clear information on how many participants used the drug, so they were excluded from the analysis. The median was used to categorise the variable. [7]: two major strata were observed: "used" *versus* "not used". [8]: five cohorts had no clear information of what second line injectable was used, so they were excluded from the analysis. The strata were defined using median value. [9]: five cohorts had no clear information of what second line injectable was used, so they were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used". [10]: two cohorts had no clear information of what FQN was used (later or early generation), so they were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used".[11]: three cohorts had missing information, in two cohorts it was not clear what FQN used (later or early generation), in one cohort it was not clear what later generation FQN was used. All three cohorts were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used".[12]: two cohorts had no clear information of what FQN was used (later or early generation), so they were excluded from the analysis. [13]: two cohorts had no clear information of how many participants used the drug, so they were excluded from the analysis. Tercile was used to categorise the variable. [14]: two cohorts had no clear information of how many participants used the drug, so they were excluded from the analysis. Tercile was used to categorise the variable. [15]: two cohorts had no clear information of how many participants used the drug, so they were excluded from the analysis. The strata were defined using the two major clusters: "used" *versus* "not used". [16]: no studies reported the use of high dose isoniazid.

TABLE 5 Occurrence of severe adverse events (SAEs), attributed to specific drugs in the treatment of multidrug-resistant or extensively drug-resistant tuberculosis[#]

Drug	Arms/cohorts reporting SAE and using the drug	Patients receiving the drug	SAEs due to drug	
			Patients with SAE related to the drug	Pooled estimate[¶] % (95% CI)
Pyrazinamide	19	2023	56	2.8 (2.1–3.7)
Ethambutol	16	1325	6	0.5 (0.2–1.1)
Injectable	19	2538	184	7.3 (6.2–8.4)
Later-generation FQN	13	827	10	1.2 (0.6–2.4)
Ofx/cfx	9	1408	40	2.8 (1.9–4.1)
Thiamide	17	2106	173	8.2 (7.0–9.6)
Cycloserine	16	2140	96	4.5 (3.6–5.5)
PAS	16	1706	208	12.2 (10.6–13.9)

FQN: later-generation fluoroquinolone (includes gati/levo/moxi-floxacin); ofx/cfx: ofloxacin/ciprofloxacin; PAS: para-aminosalicylic acid. [#]: results from 19 studies (20 cohorts) that reported grade 3–4 adverse events, or drugs permanently stopped due to adverse events, and identification of the drug related to the adverse events; [¶]: pooled using Proc Glimmix in SAS – fixed-effects meta-analysis.

Another major limitation was the incomplete reporting in many of the studies. Only one-third of studies provided adequate information about laboratory methods for diagnosis and drug susceptibility testing. Information about treatment regimens was particularly poorly reported, with missing information about drugs used initially and in the continuation phase, plus the duration of these two important phases.

Despite these important limitations, the findings of this review have several interesting implications. We speculate that the nearly complete reporting of the definition of treatment outcomes reflects the effort made over a decade ago by an international collaboration to develop a consensus definition for the major treatment outcomes in MDR-TB patients [15]. This was in striking contrast to the incomplete reporting of all other information (where no international consensus effort has been attempted).

The finding of inferior results with standardised regimens compared to individualised regimens was also found in two previous reviews [5, 7], but must be interpreted with caution due to potential confounding between centres, in terms of patient populations and resources available for treatment. It is plausible that the differences seen reflect these confounding differences more than any true benefit of individualised regimens.

The poor outcomes in XDR-TB patients is consistent with the findings of previous meta-analyses [6, 94, 95]. This finding demonstrates that 10 years after the first report of XDR-TB in South Africa [96], there has been no major advance in XDR-TB treatment.

The frequency of severe adverse events ranged from less than 1% to more than 10% with each drug. These findings are similar to those of other studies in individual cohorts [19, 21, 30, 43, 59], but given that these estimates are based on large numbers of patients treated at many centres, with narrow confidence intervals, they should be generalisable to most settings. However, the reporting of drug-related adverse events was remarkably inconsistent, even though adverse events with second-line drugs is considered a major limitation of current MDR-TB therapy [16, 97]. Although most studies reported adverse events, the majority of these did not define the methods of diagnosis, grading or attribution of these adverse events. If the management of the toxicity of these second-line drugs is to improve, we suggest that an international collaboration should define a standardised approach to definition, diagnosis, grading of severity and reporting of adverse events during MDR-TB treatment, similar to past efforts to standardise outcome definitions [15].

Conclusions

Interest and published experience in MDR-TB treatment has grown rapidly in the past 7 years, but efforts to synthesise this new body of evidence are seriously hampered by the methodological limitations of most studies and incomplete reporting. We suggest that collaborative international efforts are needed to standardise the reporting of diagnostics, treatment and adverse events, as was accomplished over a decade ago for outcome definitions [15]. This effort, plus the use of stronger study designs, including individual patient data meta-analyses, registry trials or other forms of randomised trials, will help to identify safer and more effective treatment for MDR-TB.

References

1 WHO. Definitions and Reporting Framework for Tuberculosis – 2013 revision (updated December 2014). Geneva, World Health Organization, 2014.
2 WHO. Tuberculosis Report 2016. Geneva, World Health Organization, 2016.
3 Caminero JA, Sotgiu G, Zumla A, *et al.* Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. *Lancet Infect Dis* 2010; 10: 621–629.
4 Bastos ML, Hussain H, Weyer K, *et al.* Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. *Clin Infect Dis* 2014; 59: 1364–1374.
5 Orenstein EW, Basu S, Shah NS, *et al.* Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009; 9: 153–161.
6 Johnston JC, Shahidi NC, Sadatsafavi M, *et al.* Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS ONE* 2009; 4: e6914.
7 Akcakir Y. Correlates of Treatment Outcomes of Multidrug-Resistant Tuberculosis (MDR-TB): A Systematic Review and Meta-analysis [PhD dissertation]. Montreal, Department of Epidemiology and Biostatistics, McGill University, 2010.
8 Ahuja SD, Ashkin D, Avendano M, *et al.* Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012; 9: e1001300.
9 WHO. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis – 2011 update. Geneva, World Health Organization, 2011.
10 Winters N, Butler-Laporte G, Menzies D. Efficacy and safety of World Health Organization group 5 drugs for multidrug-resistant tuberculosis treatment. *Eur Respir J* 2015; 46: 1461–1470.
11 Zhang X, Falagas ME, Vardakas KZ, *et al.* Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. *J Thorac Dis* 2015; 7: 603–615.
12 Hwang TJ, Wares DF, Jafarov A, *et al.* Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. *Int J Tuberc Lung Dis* 2013; 17: 1257–1266.
13 Chang KC, Yew WW, Tam CM, *et al.* WHO group 5 drugs and difficult multidrug-resistant tuberculosis: a systematic review with cohort analysis and meta-analysis. *Antimicrob Agents Chemother* 2013; 57: 4097–4104.
14 World Health Organization. WHO Treatment Guidelines for Drug-resistant Tuberculosis. 2016 Update. Geneva, WHO Press, 2016.
15 Laserson KF, Thorpe LE, Leimane V, *et al.* Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; 9: 640–645.
16 WHO. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva, World Health Organization, 2014.
17 The World Bank. Indicator by Country. http://data.worldbank.org/country. Date last accessed: November 25, 2015.
18 WHO. Global Health Observatory Country Views. http://apps.who.int/gho/data/node.country. Date last accessed: November 28, 2015.
19 Baghaei P, Tabarsi P, Dorriz D, *et al.* Adverse effects of multidrug-resistant tuberculosis treatment with a standardized regimen: a report from Iran. *Am J Ther* 2011; 18: e29–e34.
20 Bonnet MP, Pardini M, Meacci F, *et al.* Treatment of tuberculosis in a region with high drug resistance: outcomes, drug resistance amplification and re-infection. *PLoS ONE* 2011; 6: e23081.
21 Brust JC, Shah NS, van der Merwe TL, *et al.* Adverse events in an integrated home-based treatment program for MDR-TB and HIV in Kwazulu-Natal, South Africa. *J Acquir Immune Defic Syndr* 2013; 62: 436–440.
22 Brust JC, Gandhi NR, Carrara H, *et al.* High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000–2003. *Int J Tuberc Lung Dis* 2010; 14: 413–419.
23 Brust JC, Shah NS, Scott M, *et al.* Integrated, home-based treatment for MDR-TB and HIV in rural South Africa: an alternate model of care. *Int J Tuberc Lung Dis* 2012; 16: 998–1004.
24 Chand KS, Manchanda RK, Mittal R, *et al.* Homeopathic treatment in addition to standard care in multi drug resistant pulmonary tuberculosis: a randomized, double blind, placebo controlled clinical trial. *Homeopathy* 2014; 103: 97–107.
25 Duraisamy K, Mrithyunjayan S, Ghosh S, *et al.* Does alcohol consumption during multidrug-resistant tuberculosis treatment affect outcome? A population-based study in Kerala, India. *Ann Am Thorac Soc* 2014; 11: 712–718.
26 Farley JE, Ram M, Pan W, *et al.* Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. *PLoS ONE* 2011; 6: e20436.
27 Ganzaya S, Naranbat N, Bissell K, *et al.* Countrywide audit of multidrug-resistant tuberculosis and treatment outcomes in Mongolia. *Public Health Action* 2013; 3: 333–336.
28 Hire R, Kale AS, Dakhale GN, *et al.* A prospective, observational study of adverse reactions to drug regimen for multi-drug resistant pulmonary tuberculosis in central India. *Mediterr J Hematol Infect Dis* 2014; 6: e2014061.
29 Jain K, Desai M, Solanki R, *et al.* Treatment outcome of standardized regimen in patients with multidrug resistant tuberculosis. *J Pharmacol Pharmacother* 2014; 5: 145–149.
30 Joseph P, Desai VB, Mohan NS, *et al.* Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. *Indian J Med Res* 2011; 133: 529–534.
31 Malla P, Kanitz EE, Akhtar M, *et al.* Ambulatory-based standardized therapy for multi-drug resistant tuberculosis: experience from Nepal, 2005–2006. *PLoS ONE* 2009; 4: e8313.
32 Modongo C, Sobota RS, Kesenogile B, *et al.* Successful MDR-TB treatment regimens including amikacin are associated with high rates of hearing loss. *BMC Infect Dis* 2014; 14: 542.
33 Mugabo P, Adewumi A, Theron D, *et al.* Do HIV-infection and antiretroviral therapy influence multidrug-resistant tuberculosis treatment outcomes? *Acta Clinica Belgica* 2013; 68: 456.
34 Nagaraja C, Shashibhushan BL, Asif M, *et al.* Pattern of drug-resistance and treatment outcome in multidrug-resistant pulmonary tuberculosis. *Indian J Chest Dis Allied Sci* 2012; 54: 23–26.
35 Oladimeji O, Isaakidis P, Obasanya OJ, *et al.* Intensive-phase treatment outcomes among hospitalized multidrug-resistant tuberculosis patients: results from a nationwide cohort in Nigeria. *PLoS ONE* 2014; 9: e94393.

36 Rodriguez M, Monedero I, Caminero JA, *et al.* Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. *Int J Tuberc Lung Dis* 2013; 17: 520–525.
37 Tabarsi P, Baghaei P, Jalali S, *et al.* Is standardized treatment appropriate for non-XDR multiple drug resistant tuberculosis cases? A clinical descriptive study. *Scand J Infect Dis* 2009; 41: 10–13.
38 Tabarsi P, Chitsaz E, Baghaei P, *et al.* Impact of extensively drug-resistant tuberculosis on treatment outcome of multidrug-resistant tuberculosis patients with standardized regimen: report from Iran. *Microb Drug Resist* 2010; 16: 81–86.
39 Tabarsi P, Chitsaz E, Tabatabaei V, *et al.* Revised category II regimen as an alternative strategy for retreatment of category I regimen failure and irregular treatment cases. *Am J Ther* 2011; 18: 343–349.
40 Van der Walt M, Lancaster J, Odendaal R, *et al.* Serious treatment related adverse drug reactions amongst anti-retroviral naïve MDR-TB patients. *PLoS ONE* 2013; 8: e58817.
41 Ahmad N, Javaid A, Basit A, *et al.* Management and treatment outcomes of MDR-TB: results from a setting with high rates of drug resistance. *Int J Tuberc Lung Dis* 2015; 19: 1109–1114.
42 Blöndal K, Viiklepp P, Guðmundsson LJ, *et al.* Predictors of recurrence of multidrug-resistant and extensively drug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2012; 16: 1228–1233.
43 Bloss E, Kuksa L, Holtz TH, *et al.* Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. *Int J Tuberc Lung Dis* 2010; 14: 275–281.
44 Cegielski JP, Kurbatova E, van der Walt M, *et al.* Multidrug-resistant tuberculosis treatment outcomes in relation to treatment and initial versus acquired second-line drug resistance. *Clin Infect Dis* 2016; 62: 418–430.
45 Yuen CM, Kurbatova EV, Tupasi T, *et al.* Association between regimen composition and treatment response in patients with multidrug-resistant tuberculosis: a prospective cohort study. *PLoS Med* 2015; 12: e1001932.
46 Chan PC, Huang SH, Yu MC, *et al.* Effectiveness of a government-organized and hospital-initiated treatment for multidrug-resistant tuberculosis patients – a retrospective cohort study. *PLoS ONE* 2013; 8: e57719.
47 Chang KC, Leung CC, Yew WW, *et al.* Pyrazinamide may improve fluoroquinolone-based treatment of multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2012; 56: 5465–5475.
48 Charles M, Vilbrun SC, Koenig SP, *et al.* Treatment outcomes for patients with multidrug-resistant tuberculosis in post-earthquake Port-au-Prince, Haiti. *Am J Trop Med Hyg* 2014; 91: 715–721.
49 Dawson R, Diacon AH, Everitt D, *et al.* Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet* 2015; 385: 1738–1747.
50 Dheda K, Shean K, Zumla A, *et al.* Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet* 2010; 375: 1798–1807.
51 Diacon AH, Pym A, Grobusch MP, *et al.* Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; 371: 723–732.
52 El-Din MAT, Halim HAAE, El-Tantawy AM. Adverse reactions among patients being treated for multi-drug resistant tuberculosis in Egypt from July 2006 to January 2009. *Egypt J Chest Dis Tuberc* 2015; 64: 657–664.
53 Ferrer G, Acuna-Villaorduna C, Escobedo M, *et al.* Outcomes of multidrug-resistant tuberculosis among binational cases in El Paso, Texas. *Am J Trop Med Hyg* 2010; 83: 1056–1058.
54 Gegia M, Kalandadze I, Kempker RR, *et al.* Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis. *Int J Infect Dis* 2012; 16: e391–e396.
55 Guglielmetti L, Le Dû D, Jachym M, *et al.* Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; 60: 188–194.
56 Hafkin J, Modongo C, Newcomb C, *et al.* Impact of the human immunodeficiency virus on early multidrug-resistant tuberculosis treatment outcomes in Botswana. *Int J Tuberc Lung Dis* 2013; 17: 348–353.
57 Helbling P, Altpeter E, Egger JM, *et al.* Treatment outcomes of multidrug-resistant tuberculosis in Switzerland. *Swiss Med Wkly* 2014; 144: w14053.
58 Hicks RM, Padayatchi N, Shah NS, *et al.* Malnutrition associated with unfavorable outcome and death among South African MDR-TB and HIV co-infected children. *Int J Tuberc Lung Dis* 2014; 18: 1074–1083.
59 Jana PK, Das I, Sanyal D, *et al.* The treatment outcome of multi drug resistant tuberculosis in a teaching hospital. *Intern Med J* 2009; 16: 131–136.
60 Jiang RH, Xu HB, Li L. Comparative roles of moxifloxacin and levofloxacin in the treatment of pulmonary multidrug-resistant tuberculosis: a retrospective study. *Int J Antimicrob Agents* 2013; 42: 36–41.
61 Jo KW, Lee SD, Kim WS, *et al.* Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2014; 18: 39–43.
62 Karagöz T, Yazicioğlu Moçin O, Pazarli P, *et al.* The treatment results of patients with multidrug resistant tuberculosis and factors affecting treatment outcome. *Tuberk Toraks* 2009; 57: 383–392.
63 Kempker RR, Kipiani M, Mirtskhulava V, *et al.* Acquired drug resistance in *Mycobacterium tuberculosis* and poor outcomes among patients with multidrug-resistant tuberculosis. *Emerg Infect Dis* 2015; 21: 992–1001.
64 Koh WJ, Lee SH, Kang YA, *et al.* Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2013; 188: 858–864.
65 Kvasnovsky CL, Cegielski JP, Erasmus R, *et al.* Extensively drug-resistant TB in Eastern Cape, South Africa: high mortality in HIV-negative and HIV-positive patients. *J Acquir Immune Defic Syndr* 2011; 57: 146–152.
66 Kwak N, Kim HR, Yoo CG, *et al.* Changes in treatment outcomes of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2015; 19: 525–530.
67 Laniado-Laborín R, Estrada-Guzman J, Perez H, *et al.* Treatment of multidrug-resistant tuberculosis in a high-prevalence region through a binational consortium. *Int J Tuberc Lung Dis* 2012; 16: 610–611.
68 Lee J, Lee CH, Kim DK, *et al.* Retrospective comparison of levofloxacin and moxifloxacin on multidrug-resistant tuberculosis treatment outcomes. *Korean J Intern Med* 2011; 26: 153–159.
69 Leimane V, Dravniece G, Riekstina V, *et al.* Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000–2004. *Eur Respir J* 2010; 36: 584–593.
70 Liu CH, Li L, Chen Z, *et al.* Characteristics and treatment outcomes of patients with MDR and XDR tuberculosis in a TB referral hospital in Beijing: a 13-year experience. *PLoS ONE* 2011; 6: e19399.

71 Marks SM, Flood J, Seaworth B, *et al.* Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005–2007. *Emerg Infect Dis* 2014; 20: 812–821.
72 Milanov V, Falzon D, Zamfirova M, *et al.* Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria, 2009–2010. *Int J Mycobacteriol* 2015; 4: 131–137.
73 Miller AC, Gelmanova IY, Keshavjee S, *et al.* Alcohol use and the management of multidrug-resistant tuberculosis in Tomsk, Russian Federation. *Int J Tuberc Lung Dis* 2012; 16: 891–896.
74 Modongo C, Zetola NM. Prevalence of hypothyroidism among MDR-TB patients in Botswana. *Int J Tuberc Lung Dis* 2012; 16: 1561–1562.
75 Ndjeka N, Conradie F, Schnippel K, *et al.* Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *Int J Tuberc Lung Dis* 2015; 19: 979–985.
76 O'Donnell MR, Padayatchi N, Kvasnovsky C, *et al.* Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerg Infect Dis* 2013; 19: 416–424.
77 O'Donnell MR, Pillay M, Pillay M, *et al.* Primary capreomycin resistance is common and associated with early mortality in patients with extensively drug-resistant tuberculosis in KwaZulu-Natal, South Africa. *J Acquir Immune Defic Syndr* 2015; 69: 536–543.
78 Palacios E, Franke M, Muñoz M, *et al.* HIV-positive patients treated for multidrug-resistant tuberculosis: clinical outcomes in the HAART era. *Int J Tuberc Lung Dis* 2012; 16: 348–354.
79 Pazarli P, Duman DY, Mocin OY, *et al.* The effect of smoking on treatment outcome of multidrug-resistant tuberculosis. *Turk Toraks Dergisi* 2013; 14: 93–97.
80 Pietersen E, Ignatius E, Streicher EM, *et al.* Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet* 2014; 383: 1230–1239.
81 Podewils LJ, Gler MT, Quelapio MI, *et al.* Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS ONE* 2013; 8: e70064.
82 Qazi F, Khan U, Khowaja S, *et al.* Predictors of delayed culture conversion in patients treated for multidrug-resistant tuberculosis in Pakistan. *Int J Tuberc Lung Dis* 2011; 15: 1556–1559.
83 Roberts-Witteveen A, Reinten T, Christensen A, *et al.* Multidrug-resistant tuberculosis in New South Wales, Australia, 1999–2010: a case series report. *Int J Tuberc Lung Dis* 2015; 19: 850–856.
84 Satti H, McLaughlin MM, Hedt-Gauthier B, *et al.* Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. *PLoS ONE* 2012; 7: e46943.
85 Seddon JA, Hesseling AC, Willemse M, *et al.* Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. *Clin Infect Dis* 2012; 54: 157–166.
86 Seung KJ, Becerra MC, Atwood SS, *et al.* Salvage therapy for multidrug-resistant tuberculosis. *Clin Microbiol Infect* 2014; 20: 441–446.
87 Shean K, Streicher E, Pieterson E, *et al.* Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. *PLoS ONE* 2013; 8: e63057.
88 Smith SE, Ershova J, Vlasova N, *et al.* Risk factors for acquisition of drug resistance during multidrug-resistant tuberculosis treatment, Arkhangelsk Oblast, Russia, 2005–2010. *Emerg Infect Dis* 2015; 21: 1002–1011.
89 Tang S, Tan S, Yao L, *et al.* Risk factors for poor treatment outcomes in patients with MDR-TB and XDR-TB in China: retrospective multi-center investigation. *PLoS ONE* 2013; 8: e82943.
90 Tang S, Yao L, Hao X, *et al.* Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. *Eur Respir J* 2015; 45: 161–170.
91 van Heurck R, Payen MC, De Wit S, *et al.* Epidemiology of MDR-TB in a Belgian infectious diseases unit: a 15 years review. *Acta Clin Belg* 2013; 68: 321–324.
92 Xu HB, Jiang RH, Xiao HP. Clofazimine in the treatment of multidrug-resistant tuberculosis. *Clin Microbiol Infect* 2012; 18: 1104–1110.
93 WHO. WHO Treatment Guidelines for Drug-Resistant Tuberculosis, 2016 Update. Geneva, World Health Organization, 2016.
94 Falzon D, Gandhi N, Migliori GB, *et al.* Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J* 2013; 42: 156–168.
95 Jacobson KR, Tierney DB, Jeon CY, *et al.* Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2010; 51: 6–14.
96 Gandhi NR, Moll A, Sturm AW, *et al.* Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006; 368: 1575–1580.
97 Wu S, Zhang Y, Sun F, *et al.* Adverse events associated with the treatment of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Am J Ther* 2016; 23: e521–e530.