Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

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Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

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Summary

Background Treatment outcomes for multidrug-resistant tuberculosis remain poor. We aimed to estimate the association of treatment success and death with the use of individual drugs, and the optimal number and duration of treatment with those drugs in patients with multidrug-resistant tuberculosis.

Methods In this individual patient data meta-analysis, we searched MEDLINE, Embase, and the Cochrane Library to identify potentially eligible observational and experimental studies published between Jan 1, 2009, and April 30, 2016. We also searched reference lists from all systematic reviews of treatment of multidrug-resistant tuberculosis published since 2009. To be eligible, studies had to report original results, with end of treatment outcomes (treatment completion [success], failure, or relapse) in cohorts of at least 25 adults (aged >18 years). We used anonymised individual patient data from eligible studies, provided by study investigators, regarding clinical characteristics, treatment, and outcomes. Using propensity score-matched generalised mixed effects logistic, or linear regression, we calculated adjusted odds ratios and adjusted risk differences for success or death during treatment, for specific drugs currently used to treat multidrug-resistant tuberculosis, as well as the number of drugs used and treatment duration.

Findings Of 12 030 patients from 25 countries in 50 studies, 7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died. Compared with failure or relapse, treatment success was positively associated with the use of linezolid (adjusted risk difference 0·15, 95% CI 0·11 to 0·18), levofloxacin (0·15, 0·13 to 0·18), carbapenems (0·14, 0·06 to 0·21), moxifloxacin (0·11, 0·08 to 0·14), bedaquiline (0·10, 0·05 to 0·14), and clofazimine (0·06, 0·01 to 0·10). There was a significant association between reduced mortality and use of linezolid (–0·20, –0·23 to –0·16), levofloxacin (–0·06, –0·09 to –0·04), moxifloxacin (–0·07, –0·10 to –0·04), or bedaquiline (–0·14, –0·19 to –0·10). Compared with regimens without any injectable drug, amikacin provided modest benefits, but kanamycin and capreomycin were associated with worse outcomes. The remaining drugs were associated with slight or no improvements in outcomes. Treatment outcomes were significantly worse for most drugs if they were used despite in-vitro resistance. The optimal number of effective drugs seemed to be five in the initial phase, and four in the continuation phase. In these adjusted analyses, heterogeneity, based on a simulated I^2 method, was high for approximately half the estimates for specific drugs, although relatively low for number of drugs and durations analyses.

Interpretation Although inferences are limited by the observational nature of these data, treatment outcomes were significantly better with use of linezolid, later generation fluoroquinolones, bedaquiline, clofazimine, and carbapenems for treatment of multidrug-resistant tuberculosis. These findings emphasise the need for trials to ascertain the optimal combination and duration of these drugs for treatment of this condition.

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See **Comment** pages 797 and 798

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Introduction

WHO estimated that in 2016, there were almost 600 000 new cases of multidrug-resistant tuberculosis, defined as disease due to *Mycobacterium tuberculosis* that is resistant to isoniazid and rifampin; of the 99 165 people with multidrug-resistant tuberculosis that started treatment in 2014, only 53 549 (54%) were cured.[1] These poor cure rates reflect the lengthy treatment with second-line tuberculosis drugs, which are less effective and more toxic than those used for drug-susceptible tuberculosis.[2,3] To date, there have been very few phase 3 randomised controlled trials investigating the treatment of multidrug-resistant tuberculosis, so most evidence for regimen selection is still from observational studies,[3] or individual patient data (meta-analyses of these studies).[4]

In the past decade, several experimental and observational studies have documented the use of new and repurposed drugs, such as bedaquiline,[5,6] linezolid,[7,8] delamanid, clofazimine,[9] and the carbapenems.[10,11] We assembled a database of individual records of patients treated for multidrug-resistant tuberculosis to estimate the association of treatment outcomes with use of specific anti-tuberculosis drugs, as well the optimal number and duration of treatment with those drugs.

Methods

Search strategy and selection criteria

The protocol for this study followed PRISMA guidelines and is available from the authors.

In September 2015, we did a systematic review to identify studies published between Jan 1, 2009, and Sept 15, 2015, of treatment of multidrug-resistant tuberculosis, including extensively drug-resistant tuberculosis.[12] We updated the search in April, 2016, using the same search terms in MEDLINE, Embase, and the Cochrane library (appendix p 2). We also searched reference lists from all systematic reviews of treatment of multidrug-resistant tuberculosis published since 2009. MB and ZL screened titles, abstracts, and full texts for inclusion, and differences were resolved by consensus of both authors. Eligible studies reported original results, with end of treatment outcomes (ie, success, failure or relapse, and death) for 25 or more adults with bacteriologically confirmed pulmonary multidrug-resistant tuberculosis, to avoid small series reporting unusual cases. Studies exclusively in children, or of patients treated with the short regimens, were excluded, because these were the topics of two other individual patient data meta-analyses done simultaneously.[13,14]

We invited investigators of potentially eligible studies, and investigators who participated in our earlier

Research in context

Evidence before this study

Treatment of multidrug-resistant tuberculosis (defined as resistance to at least isoniazid and rifampin) is difficult, with high mortality and low rates of cure or treatment completion.There have been ten other systematic reviews of mainly observational studies of treatment of multidrug-resistant tuberculosis in the past decade; these have produced contradictory findings, suggesting benefits of certain drugs, but not others. In 2010, we did an individual patient data meta-analysis with 9153 patients treated in 32 centres, detecting modest benefits from many commonly used second-line tuberculosis drugs. We did an aggregate data meta-analysis of all studies of multidrug-resistant tuberculosis treatment published between Jan 1, 2009, and April 30, 2016, in MEDLINE, Embase, and the Cochrane Library, which did not detect a benefit of any specific tuberculosis drugs and revealed the limitations of aggregate data meta-analysis in this context. We repeated the individual patient data meta-analysis, inviting participation of authors of studies published since 2009, with the objective of analysing a more contemporary group of patients, some of whom would have received newer or repurposed drugs.

Added value of this study

For almost all drugs for which we had adequate information, treatment outcomes were consistently better if the isolate of *Mycobacterium tuberculosis* was susceptible, rather than resistant, to the drug used. The later generation fluoroquinolones, linezolid, and bedaquiline were associated with significantly greater treatment success and lower mortality in all patients, and in the subgroup with extensive drug resistance. The carbapenems and clofazimine were associated with significantly greater treatment success in patients with multidrug resistance, but not extensive drug resistance. On the other hand, amikacin—a commonly used second-line injectable drug—had modest benefits, whereas use of kanamycin or capreomycin were associated with worse outcomes. Several other traditionally used drugs, including pyrazinamide, ethionamide, and para-aminosalicylic acid, were associated with no benefit.

Implications of all the available evidence

Our findings have two major implications. The first is the urgent need for rapid expansion, in many countries, of laboratory capacity to test isolates for resistance to all first-line tuberculosis drugs, and the most commonly used second-line drugs. This would allow individualisation of therapy and ensure that use of ineffective drugs, with their attendant toxicity and cost, is avoided. The second is that the traditionally used drugs for treatment of multidrug-resistant tuberculosis, especially oral second-line drugs and even the injectable drugs, appear to be less effective than the later generation fluoroquinolones, linezolid, bedaquiline, clofazimine, and possibly the carbapenems. Further assessment of these newer drugs in well designed randomised trials, while expanding global access to these drugs, should be urgent priorities.

meta-analysis of multidrug-resistant tuberculosis,[4] to contribute individual-level patient data. Studies were included if the investigators provided information about clinical characteristics, diagnosis (including confirmation of rifampin resistance by phenotypic testing), treatment, and outcomes. To assess potential selection bias, we compared characteristics of patients within the studies included in the meta-analysis to those of patients from studies not included in the meta-analysis, but included in the systematic review published in 2017.[12]

Investigators provided the following de-identified information for all patients: clinical information (age, sex, HIV infection, antiretroviral therapy, previous treatment with first-line or second-line tuberculosis drugs, height, weight, diabetes mellitus, cigarette smoking, and alcohol consumption), diagnostic information (sputum acid-fast bacilli microscopy results, chest radiograph findings, site of disease, and drug susceptibility tests to first-line and second-line tuberculosis drugs), treatment information (drugs used for at least 1 month, phase of treatment [initial *vs* continuation], and duration), and outcomes (defined end of treatment outcomes, relapse, and sputum culture conversion). For patients with multiple courses of treatment with first-line or second-line tuberculosis drugs, investigators provided information only for the last complete treatment course. Investigators also provided information regarding site policies for outcome definitions, drug doses, directly observed therapy, hospital admission, and laboratory methods, including the critical concentrations to define resistance. Variables of each received dataset were reformatted and mapped to one common dataset and verified with investigators, then compared with baseline characteristics reported in the original publications.

We developed a checklist of seven indicators, adapted from the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool, to assess the quality of included studies. Of these indicators, two were considered to be essential: population selection using a census (all) or random selection approach, and availability of drug susceptibility tests results to at least one fluoroquinolone and one second-line injectable medication (defined as any of amikacin, kanamycin, or capreomycin). Of the remainder, quality was judged to be adequate if the participation rate exceeded 80%, loss to follow-up was less than 20%, treatment outcomes were defined according to published guidelines,[15,16] and more than 90% of patient records had information about HIV infection, previous tuberculosis treatment, and age—all important determinants of outcomes.[4] Participation rates were based on the reported total number of eligible patients and the number enrolled, although if the investigators stated that all patients with multidrug-resistant tuberculosis were enrolled, we considered the participation rate to be 100%. Studies of high quality met both essential criteria and at least four of the other six. Studies of moderate quality met one of the two essential parameters and at least five in total. Remaining studies were considered of low quality.

Data analysis

We assessed end of treatment success (defined as cure or completion), compared with failure or relapse; and death from any cause during tuberculosis treatment, compared with success or failure or relapse. These treatment outcomes were defined according to WHO[16] or Laserson and colleagues[15] in 47 studies (appendix, p 4). We did not combine the outcomes of death and failure or relapse, because these cannot be considered as equivalent.

We analysed the association of each drug with success and death in patients with *M tuberculosis* isolates with confirmed susceptibility, or resistance to that drug. We assumed all isolates were susceptible to carbapenems, bedaquiline, linezolid, or clofazimine unless there was documented resistance. For all other drugs, if drug susceptibility test results were missing, susceptibility was assumed if more than 90% of isolates from other patients at the same centre were confirmed as being susceptible to that drug. For the analysis of the number of possibly effective drugs, we counted drugs with published evidence from randomised trials of effectiveness. Possibly effective drugs were: ethambutol, pyrazinamide, all injectable drugs and fluoroquinolones, ethionamide and protionamide, cycloserine and terizidone, and para-aminosalicylic acid, if there were tests showing susceptibility to those drugs; clofazimine, linezolid, carbapenems, bedaquiline, and delamanid were considered if the patient was susceptible, or there was no drug susceptibility test for that drug. We did not count amoxicillin and clavulanic acid (in the absence of a carbapenem), and macrolides, because there is no published evidence of their efficacy against tuberculosis.

For the analysis of each drug, patients were included if they received at least 1 month of the drug. Patients who received two or more fluoroquinolones, or two or more injectable drugs, were excluded from analysis of the respective drug classes because treatment outcomes could not be attributed to one of the drugs. Linezolid, clofazimine, bedaquiline, amoxicillin and clavulanic acid, macrolides, and the carbapenems were used only in some centres, and often for a minority of patients in those centres. Therefore, patients who received each of these six drugs were compared with patients who were treated at centres where that drug was not used at all, to reduce potential confounding by indication.[17,18]

For the analyses of optimum duration of initial treatment phase, or total treatment duration, we excluded patients who died or were lost to follow-up during treatment because these outcomes determined the duration of individualised regimens. We defined the start of treatment for multidrug-resistant tuberculosis as the date on which one or more second-line tuberculosis drugs were started, and the duration of the initial phase was defined as the duration of injectable drugs. Sputum

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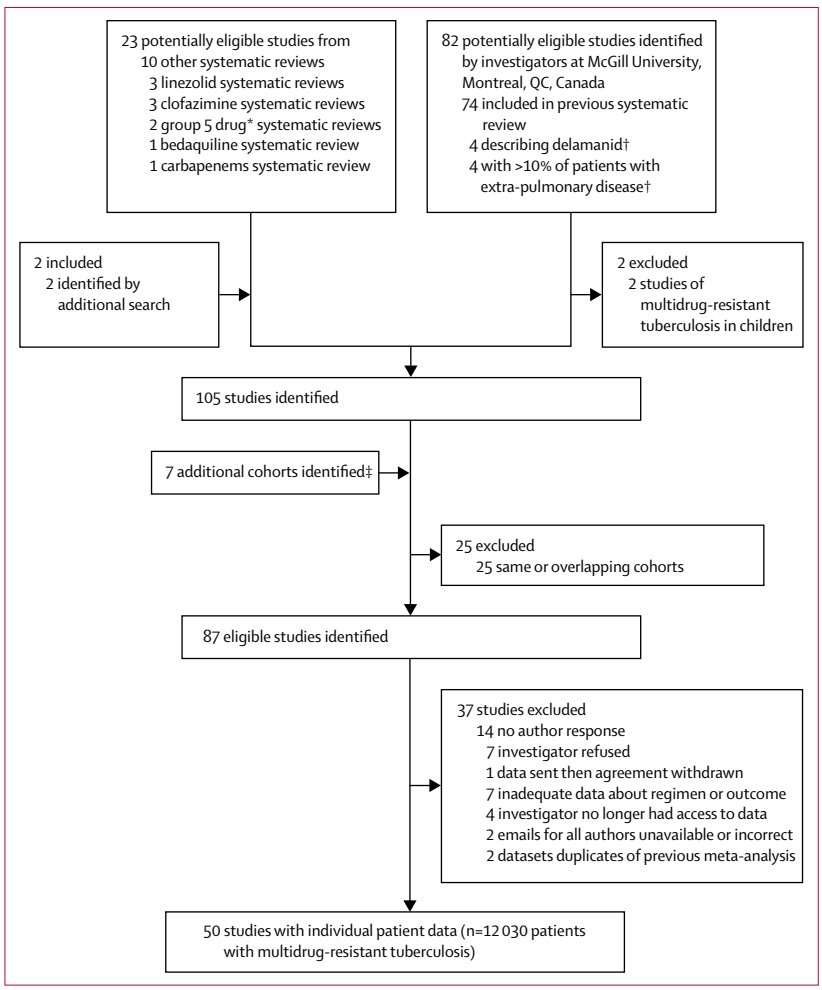

Figure: **Study selection**
*According to WHO definition. †Not eligible for previous meta-analysis but eligible for this study. ‡Investigators of the 31 cohorts from the previous meta-analysis were contacted, from whom these new and additional cohorts were identified.

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culture conversion was defined as two consecutive negative sputum cultures, at least 30 days apart; the date of conversion was the date of specimen collection for the earlier negative culture.

We used propensity score matching[19] (caliper method with difference of 0·02 allowed, 1:1 matching with replacement) based on individual-level covariates of age, sex, HIV co-infection, acid-fast bacilli smear results, cavitation on chest radiographs, history of tuberculosis treatment with first-line or second-line tuberculosis drugs, and number of possibly effective drugs in the initial phase. In the analysis of number of effective drugs, we did not adjust estimates for the number of effective drugs. For the analysis of individual drugs, we also adjusted for resistance to fluoroquinolones or second-line injectable drugs, unless the drugs of interest were the fluoroquinolones or second-line injectable drugs themselves, or the analysis was restricted to the subgroup with extensive drug resistance. We used a random-effects (random intercept and random slope for matched pairs) generalised logistic mixed effects model (PROC GLIMMIX in SAS) to estimate adjusted odds ratios (ORs) and 95% CIs of success (versus failure or relapse, but not death) or death (versus success) during treatment associated with use of specific drugs, or with number of drugs, or duration of treatment. We calculated adjusted risk differences and 95% CIs with fixed effects generalised linear models with identity link, adjusted for the propensity score, because the random effects models did not converge. For propensity score matching only, we imputed missing patient characteristics from the mean values of other patients at the same centre. We estimated I^2 for the adjusted ORs using a generalised linear mixed model with a simulation-based approach.[20] I^2 was not calculated for some adjusted ORs because τ^2, on which I^2 is based, could not be estimated in SAS.

We did sensitivity analyses in subgroups of patients treated at centres in high-income, upper-middle-income, and low and low-middle-income countries, or with additional resistance to any fluoroquinolone or any second-line injectable drug, or both (ie, had extensive drug resistance).

We did all analyses using SAS (version 9.4).

This study was approved by an ethics committee of the Research Institute of the McGill University Health Center. Ethics approval was also obtained at participating sites, if considered necessary.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 87 individual studies, of which 50 (57%) provided adequate data for patients with confirmed pulmonary rifampin resistance (n=12 030; figure).[5,7,8,10,11,21–77] Of these patients, 11 918 (99·1%) had documented isoniazid resistance, 31 (0·3%) had isoniazid-susceptible isolates, and another 81 (0·7%) did not have drug susceptibility tests to isoniazid, and these 112 patients were considered together with all others with multidrug-resistant tuberculosis in all analyses. Relapse was ascertained in only 16 (32%) studies with 2509 patients. The characteristics of the study settings, such as laboratory methods and usual drug doses, and quality assessment of the 50 included studies are summarised in the appendix (pp 4–21). Quality was judged as being high in 39 studies, moderate in nine studies, and low in two studies. Characteristics of the patients included in this meta-analysis were similar to those of patients within studies that had been originally identified as being potentially eligible, but who were not included (appendix, pp 23–26).

	Treatment success (n=7346)	Failed treatment or relapsed (n=1017)	Died during treatment (n=1729)	Did not complete (patient decision, data lost, outcome unknown, or patient transferred; n=1938)
All patients	65% (59–70)	6% (5–8)	11% (8–14)	12% (10–15)
Disease category*				
No second-line drug susceptibility testing†	66% (60–72)	6% (4–9)	12% (9–14)	15% (9–26)
Sensitive to second-line injectable drugs and fluoroquinolones‡	73% (68–77)	4% (3–6)	9% (7–11)	12% (9–16)
Resistant to second-line injectable drugs (before extensive drug resistance)§	62% (56–67)	9% (7–11)	12% (9–16)	17% (13–21)
Resistant to fluoroquinolones (before extensive drug resistance)§	57% (52–63)	13% (9–19)	12% (9–16)	14% (9–19)
Resistant to second-line injectable drugs and fluoroquinolones (extensively drug resistant)¶	51% (41–62)	14% (10–19)	16% (10–23)	12% (9–17)
HIV status				
HIV positive, not receiving antiretroviral therapy	34% (24–46)	10% (6–16)	29% (17–44)	20% (15–27)
HIV positive, receiving antiretroviral therapy	55% (43–66)	4% (2–8)	26% (18–34)	12% (8–17)
HIV negative	68% (62–73)	7% (5–9)	9% (8–12)	12% (9–15)
Country income level				
Low and low-middle income	71% (68–74)	6% (3–11)	11% (8–16)	9% (5–16)
Upper-middle income	51% (41–61)	9% (6–12)	17% (11–25)	16% (11–22)
High income	75% (71–79)	4% (3–7)	6% (4–9)	11% (8–15)

Data are pooled cumulative percentage (95% CI), estimated with the random effect (at study level) method. Percentages do not total 100% in all cases. *Multidrug-resistant tuberculosis categories are based on susceptibility to second-line injectable drugs and fluoroquinolones. †No drug susceptibility test results for both second-line injectable drugs and fluoroquinolones. ‡Susceptible to all second-line injectable drugs and fluoroquinolones. §Patients resistant to one drug type, but susceptible to the other (second-line injectable drugs or fluoroquinolones). ¶Extensively drug resistant defined as multidrug resistance plus resistance to a second-line injectable drug and a fluoroquinolone.

Table 1: **Pooled outcomes from aggregate data meta-analysis, overall and stratified by major covariate**

	Success *vs* failure or relapse	Died *vs* success, failure, or relapse	Did not complete *vs* success, failure, relapse, died
Age (per 1 year older)	1·0 (0·99–1·01)	1·02 (1·01–1·02)	0·99 (0·99–0·99)
Sex (reference: female)	1·0 (0·9–1·1)	1·1 (1·0–1·3)	1·4 (1·3–1·6)
HIV positive (reference: HIV negative)	0·9 (0·7–1·2)	3·1 (2·6–3·7)	1·2 (1·0–1·4)
Acid-fast bacilli smear (reference: acid-fast bacilli negative)	0·5 (0·4–0·6)	1·5 (1·2–1·8)	1·0 (0·9–1·2)
Cavitation on chest radiograph (reference: no cavity)	0·6 (0·5–0·7)	1·4 (1·2–1·6)	1·0 (0·9–1·2)
Previous tuberculosis treatment with first-line drugs (reference: no previous first-line drug treatment)	0·6 (0·5–0·8)	1·1 (0·9–1·3)	1·1 (0·9–1·3)
Previous tuberculosis treatment with second-line drugs (reference: no previous second-line drug treatment)	0·6 (0·5–0·8)	1·1 (0·9–1·4)	0·9 (0·8–1·1)
Fluoroquinolone resistance* (reference: sensitive to fluoroquinolone)	0·3 (0·2–0·4)	1·4 (1·2–1·8)	1·0 (0·8–1·2)
Resistance to any second-line injectable drug* (reference: sensitive to second-line injectable drug)	0·6 (0·5–0·8)	1·6 (1·3–1·9)	1·0 (0·9–1·2)
Pyrazinamide resistance* (reference: sensitive to pyrazinamide)	0·8 (0·6–1·1)	1·3 (1·0–1·7)	0·8 (0·7–1·0)
Ethambutol resistance* (reference: sensitive to ethambutamol)	1·0 (0·8–1·4)	1·2 (1·0–1·5)	0·9 (0·8–1·0)

Data are adjusted odds ratio (95% CI). All estimates are adjusted for age, sex, HIV status, acid-fast bacilli smear, cavitation on chest x-ray, previous tuberculosis treatment with first-line or second-line tuberculosis drugs, and resistance to fluoroquinolones or second-line injectable drugs (except in analyses stratified by resistance to those drugs). *Assessed with drug susceptibility testing.

Table 2: **Association of covariates with outcome**

The mean age of patients was 38·3 years (SD 13·8), 289 (2·4%) were children, 7586 (63%) of 12 028 were male, and 1833 (18·3%) of 10 021 patients tested were HIV positive, of whom 906 (49%) were receiving antiretroviral therapy (appendix, p 23). 8128 (78·5%) of 10 467 had been previously treated for tuberculosis, and 1618 (25·7%) of 6305 had previously received second-line drugs. Of the isolates tested, about half were resistant to pyrazinamide, streptomycin, or ethambutol, about a quarter were resistant to any of the second-line injectable drugs or to a fluoroquinolone (appendix, p 24), and 1281 (10·6% of all patients) had extensive drug resistance.

In total, 7346 (61%) patients were cured or successfully completed treatment, 1017 (8%) had failure or relapsed,

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	Drug given (events/total)	Drug not given (events/total)	Crude OR (95% CI)	Propensity score matched multivariate regression			
				Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
Ethambutol							
Susceptible strains							
Success	2374/2605	588/667	1·4 (1·1–1·8)	2598	0·9 (0·7–1·1)	5·2%	–0·01 (–0·03 to 0·01)
Death	397/3002	95/762	1·1 (0·8–1·4)	3001	1·0 (0·9–1·2)	NC	0·00 (–0·02 to 0·02)
Resistant strains							
Success	874/1040	3064/3489	0·7 (0·6–0·9)	1040	0·8 (0·6–1·1)	NC	–0·02 (–0·05 to 0·01)
Death	307/1347	599/4088	1·7 (1·5–2·0)	1344	1·7 (1·4–2·1)	NC	0·07 (0·04 to 0·10)
Pyrazinamide							
Susceptible strains							
Success	1683/1818	249/268	1·0 (0·6–1·6)	1818	0·7 (0·5–0·9)	NC	–0·03 (–0·04 to –0·01)
Death	168/1986	39/307	0·6 (0·4–0·9)	1986	0·7 (0·6–0·8)	NC	–0·03 (–0·05 to –0·01)
Resistant strains							
Success	925/1065	1043/1143	0·6 (0·5–0·8)	1064	0·5 (0·4–0·7)	18·0%	–0·05 (–0·08 to –0·03)
Death	197/1262	133/1276	1·6 (1·3–2·0)	1262	1·5 (1·2–1·9)	31·2%	0·05 (0·02 to 0·07)
Ethionamide or protionamide							
Susceptible strains							
Success	3027/3435	306/339	0·8 (0·6–1·2)	3434	0·8 (0·7–0·9)	NC	–0·02 (–0·04 to –0·01)
Death	628/4063	55/394	1·1 (0·8–1·5)	4062	0·9 (0·8–1·0)	NC	–0·00 (–0·02 to 0·01)
Resistant strains							
Success	893/1082	426/486	0·7 (0·5–0·9)	1082	0·6 (0·5–0·8)	32·6%	–0·06 (–0·09 to –0·03)
Death	209/1291	72/558	1·3 (1·0–1·7)	1291	1·8 (1·4–2·2)	NC	0·06 (0·04 to 0·09)
Cycloserine or terizidone							
Susceptible strains							
Success	5017/5684	984/1160	1·3 (1·1–1·6)	5682	1·5 (1·4–1·7)	34·1%	0·05 (0·03 to 0·06)
Death	1065/6749	415/1575	0·5 (0·5–0·6)	6744	0·6 (0·5–0·6)	34·4%	–0·09 (–0·10 to –0·07)
Resistant strains							
Success	217/273	129/144	0·5 (0·2–0·8)	257	0·7 (0·4–1·1)	NC	–0·04 (–0·10 to 0·01)
Death	76/349	20/164	2·0 (1·2–3·4)	331	0·9 (0·6–1·3)	NC	0·02 (–0·04 to 0·09)
Para-aminosalicylic acid							
Susceptible strains							
Success	2230/2605	2865/3272	0·8 (0·7–1·0)	2605	0·8 (0·7–1·0)	0·2%	–0·01 (–0·03 to 0·01)
Death	702/3307	678/3950	1·3 (1·2–1·5)	3307	1·2 (1·1–1·4)	68·1%	0·02 (0·00 to 0·04)
Resistant strains							
Success	244/298	295/334	0·6 (0·4–0·9)	297	0·8 (0·5–1·2)	NC	–0·04 (–0·10 to 0·02)
Death	50/348	32/366	1·8 (1·1–2·8)	346	2·3 (1·4–3·9)	NC	0·08 (0·04 to 0·12)
Streptomycin*							
Susceptible strains							
Success	959/1017	406/455	2·0 (1·3–3·0)	1017	1·5 (1·1–2·1)	NC	0·02 (–0·00 to 0·04)
Death	104/1121	78/533	0·6 (0·4–0·8)	1121	0·8 (0·6–1·1)	NC	–0·02 (–0·04 to 0·01)
Resistant strains							
Success	81/93	406/455	0·8 (0·4–1·6)	87	0·3 (0·1–1·1)	NC	–0·09 (–0·17 to –0·01)
Death	19/112	78/533	1·2 (0·7–2·1)	109	0·8 (0·4–1·6)	NC	–0·03 (–0·14 to 0·07)
Amikacin*							
Susceptible strains							
Success	1302/1394	406/455	1·7 (1·2–2·5)	1393	2·0 (1·5–2·6)	9·4%	0·06 (0·04 to 0·08)
Death	250/1644	78/533	1·0 (0·8–1·4)	1644	1·0 (0·8–1·2)	NC	–0·00 (–0·03 to 0·02)
Resistant strains							
Success	100/110	406/455	1·2 (0·6–2·5)	110	0·5 (0·2–1·5)	NC	–0·06 (–0·13 to 0·02)
Death	25/135	78/533	1·3 (0·8–2·2)	134	1·1 (0·6–2·0)	NC	–0·01 (–0·11 to 0·08)

(Table 3 continues on next page)

	Drug given (events/total)	Drug not given (events/total)	Crude OR (95% CI)	Propensity score matched multivariate regression			
				Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
(Continued from previous page)							
Kanamycin*							
Susceptible strains							
Success	2192/2523	406/455	0·8 (0·6–1·1)	2523	0·5 (0·4–0·6)	52·9%	−0·07 (−0·08 to −0·05)
Death	435/2958	78/533	1·0 (0·8–1·3)	2958	1·1 (0·9–1·2)	22·9%	0·01 (−0·01 to 0·02)
Resistant strains							
Success	118/156	406/455	0·4 (0·2–0·6)	155	0·3 (0·1–0·6)	32·7%	−0·15 (−0·24 to −0·07)
Death	41/197	78/533	1·5 (1·0–2·3)	194	2·1 (1·2–3·8)	3·2%	0·10 (0·03 to 0·17)
Capreomycin*†							
Susceptible strains							
Success	821/938	406/455	0·8 (0·6–1·2)	938	0·8 (0·6–1·1)	NC	−0·03 (−0·06 to 0·00)
Death	176/1114	78/533	1·1 (0·8–1·5)	1114	1·4 (1·1–1·7)	NC	0·04 (0·01 to 0·07)
Resistant strains							
Success	186/222	406/455	0·6 (0·4–1·0)	216	0·8 (0·5–1·4)	NC	−0·03 (−0·09 to 0·04)
Death	42/264	78/533	1·1 (0·7–1·7)	261	2·1 (1·2–3·6)	NC	0·08 (0·02 to 0·13)
Ciprofloxacin‡							
Susceptible strains							
Success	226/230	258/355	21·2 (7·7–58·7)	210	7·9 (2·7–23·2)	NC	0·09 (0·04 to 0·14)
Death	51/281	292/647	0·3 (0·2–0·4)	263	1·4 (0·9–2·2)	NC	0·09 (0·03 to 0·15)
Ofloxacin‡							
Susceptible strains							
Success	1563/1865	258/355	1·9 (1·5–2·5)	1865	1·0 (0·8–1·2)	54·1%	−0·01 (−0·04 to 0·01)
Death	420/2285	292/647	0·3 (0·2–0·3)	2285	0·6 (0·5–0·7)	19·1%	−0·08 (−0·11 to −0·06)
Levofloxacin‡							
Susceptible strains							
Success	1361/1450	258/355	5·7 (4·2–7·9)	1450	4·2 (3·3–5·4)	25·8%	0·15 (0·13 to 0·18)
Death	182/1632	292/647	0·2 (0·1–0·2)	1632	0·6 (0·5–0·7)	NC	−0·06 (−0·09 to −0·04)
Moxifloxacin‡							
Susceptible strains							
Success	974/1031	258/355	6·4 (4·5–9·2)	1031	3·8 (2·8–5·2)	21·3%	0·11 (0·08 to 0·14)
Death	114/1145	292/647	0·1 (0·1–0·2)	1145	0·5 (0·4–0·6)	33·4%	−0·07 (−0·10 to −0·04)
Levofloxacin or moxifloxacin *vs* ofloxacin‡							
Strains resistant to ofloxacin, and not resistant to levofloxacin or moxifloxacin							
Success	581/726§	59/98¶	2·6 (1·7–4·1)	715	1·7 (1·3–2·2)	31·1%	0·08 (0·04 to 0·13)
Death	202/928§	60/158¶	0·5 (0·3–0·6)	927	0·9 (0·8–1·2)	NC	0·02 (−0·01 to 0·06)
Linezolid‖							
Susceptible strains**							
Success	722/799	5066/5864	1·5 (1·2–1·9)	799	3·4 (2·6–4·5)	55·6%	0·15 (0·11 to 0·18)
Death	84/883	1456/7320	0·4 (0·3–0·5)	883	0·3 (0·2–0·3)	77·0%	−0·20 (−0·23 to −0·16)
Clofazimine							
Susceptible strains**							
Success	485/564	5321/6106	0·9 (0·7–1·2)	564	1·5 (1·1–2·1)	28·7%	0·06 (0·01 to 0·10)
Death	115/679	1292/7398	1·0 (0·8–1·2)	679	0·8 (0·6–1·0)	NC	−0·04 (−0·08 to 0·00)
Amoxicillin-clavulanic acid							
No drug susceptibility testing							
Success	768/972	3443/3943	0·5 (0·5–0·7)	972	0·6 (0·5–0·8)	NC	−0·07 (−0·10 to −0·03)
Death	234/1206	717/4660	1·3 (1·1–1·6)	1206	1·7 (1·3–2·1)	80·6%	0·06 (0·04 to 0·09)

(Table 3 continues on next page)

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See **Online** for appendix

	Drug given (events/total)	Drug not given (events/total)	Crude OR (95% CI)	Propensity score matched multivariate regression			
				Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
(Continued from previous page)							
Macrolides							
No drug susceptibility testing							
Success	560/723	2628/3093	0·6 (0·5–0·7)	722	0·6 (0·5–0·8)	10·9%	–0·08 (–0·12 to –0·03)
Death	185/908	562/3655	1·4 (1·2–1·7)	908	1·6 (1·2–2·0)	75·3%	0·06 (0·02 to 0·09)
Bedaquiline							
No drug susceptibility testing**							
Success	431/491	6312/7220	1·0 (0·8–1·4)	490	2·0 (1·4–2·9)	NC	0·10 (0·05 to 0·14)
Death	59/550	1569/8789	0·6 (0·4–0·7)	548	0·4 (0·3· 0·5)	33·5%	–0·14 (–0·19 to –0·10)
Imipenem and meropenem (carbapenems)							
No drug susceptibility testing**							
Success	130/139	6871/7861	2·1 (1·1–4·1)	138	4·0 (1·7–9·1)	57·8%	0·14 (0·06 to 0·21)
Death	30/169	1674/9535	1·0 (0·7–1·5)	168	1·0 (0·5–1·7)	NC	–0·00 (–0·09 to 0·08)

The analyses were done in patients with isolates with confirmed susceptibility or resistance to each drug. For the analysis of the injectable drugs, 613 individuals did not receive any injectable drug, and we excluded 857 other patients who received two drugs or more. We included 192 patients in this analysis who were switched to a second-line injectable drug from streptomycin because they had isolates that were streptomycin-resistant and susceptible to the second-line injectable, and these patients were analysed as receiving a second-line injectable drug. For the analysis of fluoroquinolones, 828 patients received two or more fluoroquinolones and were excluded from analyses of effect of specific fluoroquinolones on outcomes. The dose of levofloxacin was 750–1000 mg per day in 33 of 36 studies reporting use of this drug, and the dose of moxifloxacin was 400 mg per day in 28 of 32 studies reporting use of this drug. Results were adjusted as described in the Methods. OR=odds ratio. RD=risk difference. NC=not calculated. *Injectable drug; denominator is number of patients who did not receive any injectable drug. †1838 patients received capreomycin and no other second-line injectable drug (77% of all patients receiving capreomycin) at 18 centres where this was the most commonly used second-line injectable drug. ‡Fluoroquinolone; denominator is number of patients who did not receive any fluoroquinolone. §Levofloxacin or moxifloxacin used. ¶Ofloxacin used. ||Used in 38 studies. The initial dose of linezolid was 1200 mg for 91 patients in five studies, 600 mg for 784 patients in 28 studies, and 300 mg for 99 patients in five studies. **If drug susceptibility tests were not done, isolates were assumed as being susceptible to these drugs (see Methods).

Table 3: **Association of each drug with treatment success and death during treatment**

1729 (14%) died, and the remainder of patients (1938 [16%]) decided to stop therapy, were lost to follow-up, were transferred, or otherwise had unknown outcomes. Using aggregate data at study level, the overall pooled success rate was 65%, failure and relapse rate was 6%, and death rate was 11% (table 1). Patients with extensively drug-resistant tuberculosis had the highest failure or relapse rates (14%), and HIV-positive individuals had the highest mortality, particularly those not receiving antiretroviral therapy (29%; table 1).

Treatment success or death were both associated with positive acid-fast bacilli smears, cavitation on chest radiographs, and resistance to fluoroquinolones or a second-line injectable drug (table 2). Death was also associated with HIV infection, whereas success was also associated with history of tuberculosis treatment with first-line or second-line drugs (table 2). These associations supported our decision to adjust for these variables in all regression analyses.

Thioacetazone, delamanid, and rifabutin could not be analysed because of small numbers of patients receiving these drugs in the data we received (appendix, p 25). In adjusted analyses, use of ethambutol, ethionamide and protionamide, or para-aminosalicylic acid were associated with no benefit in patients with susceptible isolates, and worse outcomes in patients with resistant isolates (table 3). Use of pyrazinamide was associated with lower mortality (adjusted risk difference –0·03, 95% CI –0·05 to –0·01) if isolates were susceptible, but significantly less success (–0·05, –0·08 to –0·03) and higher mortality (0·05, 0·02 to 0·07) if isolates were resistant. Use of cycloserine or terizidone was beneficial in patients with susceptible isolates, but not in patients with resistant isolates (table 3).

Compared with the 613 individuals who received no injectable drugs, use of amikacin in people with susceptible strains was associated with greater success (adjusted risk difference 0·06, 95% CI 0·04 to 0·08) but no difference in death, whereas use of kanamycin was associated with significantly lower success (–0·07, –0·08 to –0·05) but no difference in death (0·01, –0·01 to 0·02), and capreomycin use with lower success (–0·03, –0·06 to 0·00) and more deaths (0·04, 0·01 to 0·07; table 3). Of the 2387 capreomycin-treated patients, 1838 (77%) received no other second-line injectable drug and were treated in centres where capreomycin was the most commonly used second-line injectable drug.

Compared with 734 patients who received no fluoroquinolones, use of ofloxacin was associated with no difference in treatment success, but lower mortality (adjusted risk difference –0·08, 95% CI –0·11 to –0·06), whereas use of levofloxacin or moxifloxacin was associated with significantly greater success (0·15, 0·13 to 0·18 for levofloxacin and 0·11, 0·08 to 0·14 for moxifloxacin) and lower mortality (–0·06, –0·09 to –0·04 for levofloxacin

and –0·07, –0·10 to –0·04 for moxifloxacin). Among individuals whose isolates were resistant to ofloxacin, success was significantly greater if they received levofloxacin or moxifloxacin compared with ofloxacin (0·08, 0·04 to 0·13).

Significantly greater success was seen with use of linezolid (adjusted risk difference 0·15, 0·11 to 0·18), bedaquiline (0·10, 0·05 to 0·14), clofazimine (0·06, 0·01 to 0·10), and the carbapenems (0·14, 0·06 to 0·21), compared with non-use of each drug. Significant reduction in death was associated with use of linezolid (–0·20, –0·23 to –0·16) and bedaquiline (–0·14, –0·19 to –0·10), but not with use of clofazimine or the carbapenems (table 3). Use of amoxicillin-clavulanic acid or a macrolide were both associated with significantly less success and greater mortality (table 3). For some of these analyses, the estimated heterogeneity exceeded 50%, which is considered high.

In sensitivity analyses, results were essentially unchanged within subgroups of patients with fluoroquinolone resistance, or second-line injectable drug resistance alone (pre-extensive drug resistance), or when controls were selected from all centres (data not shown). When analyses were stratified by country income level, findings with the new or repurposed drugs were also unchanged, but findings with regard to injectables were different in that kanamycin, in particular, was not associated with worse outcomes within low-middle income countries (data not shown).

In patients with extensive drug resistance, use of capreomycin, regardless of drug susceptibility test result, was associated with significantly lower success (adjusted risk difference –0·14, –0·20 to –0·07) and increased mortality (0·25, 0·20 to 0·30; table 4). Use of moxifloxacin or levofloxacin was associated with reduced mortality, even though all isolates (by definition) were resistant to fluoroquinolones. Linezolid and bedaquiline were both associated with significantly greater success and lower mortality rate, whereas clofazimine was associated with lower mortality rate only (table 4).

The maximal odds of success with lowest odds of mortality was seen with use of at least five drugs in the initial phase, and at least four drugs in the continuation phase (table 5).

Initial phase duration was analysed in 6858 patients, among whom the odds of success were maximal with an initial phase lasting 6–8 months (mean 7·9 months; table 6). The interval between sputum culture conversion and the end of the initial phase was analysed in 4122 patients, among whom the odds of success were maximal with intervals of 5–7 months (mean 5·9 months; table 6). Total duration of treatment was analysed in 7832 patients, among whom the optimal duration was 19–22 months (mean 21 months; table 6). The interval from sputum culture conversion to end of treatment was analysed in 4535 patients, in whom the optimal interval was 15–18 months (mean 16·9 months; table 6).

	Drug given (events/total)	Drug not given (events/total)	Propensity score matched multivariate regression			
			Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
Injectables						
Amikacin*						
Success	62/69	384/551	68	2·5 (0·9–6·6)	NC	0·09 (–0·04 to 0·22)
Death	15/84	395/946	83	0·4 (0·2–0·8)	NC	–0·16 (–0·30 to –0·03)
Kanamycin†						
Success	52/74	394/546	73	0·9 (0·5–1·9)	15·1%	–0·01 (–0·16 to 0·14)
Death	19/93	391/937	93	0·9 (0·5–1·9)	40·5%	–0·01 (–0·13 to 0·10)
Capreomycin (all patients)						
Success	217/338	229/282	332	0·5 (0·4–0·7)	3·7%	–0·14 (–0·20 to –0·07)
Death	354/692	56/338	675	3·4 (2·7–4·3)	NC	0·25 (0·20 to 0·30)
Capreomycin (sensitive patients only)						
Success	72/91	229/282	91	0·8 (0·4–1·7)	6·0%	–0·04 (–0·16 to 0·08)
Death	25/116	56/338	115	3·8 (1·6–8·9)	NC	0·16 (0·07 to 0·25)
Other drugs						
Levofloxacin or moxifloxacin‡						
Success	279/360	119/182	359	1·2 (0·8–1·6)	7·7%	0·01 (–0·05 to 0·06)
Death	122/482	253/435	482	0·6 (0·4–0·8)	NC	–0·07 (–0·12 to –0·02)
Linezolid						
Success	255/281	221/392	280	6·6 (4·1–10·6)	7·3%	0·31 (0·24 to 0·38)
Death	33/314	418/810	314	0·2 (0·1–0·3)	7·5%	–0·29 (–0·36 to –0·23)
Clofazimine						
Success	141/173	335/500	173	1·5 (0·9–2·6)	NC	0·04 (–0·04 to 0·13)
Death	43/216	408/908	216	0·4 (0·2–0·6)	19·7%	–0·18 (–0·27 to –0·10)
Bedaquiline						
Success	126/145	350/528	139	2·5 (1·3–4·8)	NC	0·12 (0·03 to 0·21)
Death	18/163	433/961	155	0·5 (0·2–0·9)	NC	–0·09 (–0·17 to –0·02)

The analyses were done for all patients with extensively drug-resistant tuberculosis, and all patients who received each drug were compared with all patients who did not receive that drug. Patients who switched injectable drugs were excluded, as were patients who switched fluoroquinolones. OR=adjusted odds ratio. RD=adjusted risk difference. NC=not calculated. *Of the 84 patients that received amikacin, 39 were susceptible. †Of the 93 patients who received kanamycin, 12 were susceptible. ‡All of these patients were resistant to ofloxacin; only 175 had drug susceptibility testing results to later generation fluoroquinolones, and all of them were resistant.

Table 4: **Association of selected drugs used in extensively drug-resistant tuberculosis with success and death**

Discussion

We assessed 50 datasets from 25 countries, with 12 030 patients treated for multidrug-resistant tuberculosis. Of the drugs analysed, levofloxacin, moxifloxacin, linezolid, and bedaquiline were associated with greater treatment success and reduced death. Clofazimine and the carbapenems were associated with significantly improved treatment success but not reduced death. Pyrazinamide, streptomycin, amikacin, and cycloserine and terizidone were associated with modest benefits, but only in patients with susceptible isolates, whereas the use of kanamycin, capreomycin, ethionamide and protionamide, para-aminosalicylic acid, the macrolides, and amoxicillin-clavulanic acid (when used without carbapenems), were associated with no significant benefit or significantly worse outcomes.

Despite the large number of patients, this study had weaknesses, particularly the observational design and individualised treatment policies in most studies; this

	Success/total	Death/total	Propensity score matched multivariate regression			
			Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
Initial phase						
Success *vs* failure or relapse						
0–2 drugs	1428/1742	NA	..	1 (ref)	..	..
3 drugs	1659/1891	NA	1891	1·8 (1·5–2·1)	0·2%	0·08 (0·06 to 0·10)
4 drugs	1996/2243	NA	2243	2·0 (1·8–2·4)	0·1%	0·09 (0·07 to 0·10)
5 drugs	1152/1262	NA	1262	2·6 (2·1–3·2)	0·1%	0·12 (0·10 to 0·14)
>6* drugs	587/642	NA	642	2·7 (2·0–3·6)†	0·1%	0·14 (0·10 to 0·17)†
Died *vs* success, failure, or relapse (≥6)						
0–2 drugs	NA	524/2266	..	1 (ref)	..	..
3 drugs	NA	333/2224	2223	0·6 (0·6–0·7)	17·0%	–0·06 (–0·08 to –0·05)
4 drugs	NA	423/2666	2666	0·7 (0·6–0·8)	17·5%	–0·04 (–0·06 to –0·03)
5 drugs	NA	141/1403	1403	0·4 (0·3–0·5)†	13·1%	–0·14 (–0·16 to –0·12)†
>6* drugs	NA	66/708	708	0·4 (0·3–0·5)†	11·9%	–0·19 (–0·22 to –0·15)†
Continuation phase						
Success *vs* failure or relapse						
0–1 drugs	1264/1528	NA	..	1 (ref)	..	..
2 drugs	1591/1807	NA	1807	1·6 (1·4–1·9)	NC	0·06 (0·04 to 0·08)
3 drugs	1934/2177	NA	2177	1·7 (1·5–2·0)	NC	0·05 (0·03 to 0·07)
4 drugs	1017/1097	NA	1097	2·8 (2·2–3·5)†	NC	0·13 (0·11 to 0·15)†
>5 drugs	422/476	NA	476	1·7 (1·3–2·3)	NC	0·13 (0·09 to 0·16)†
Died *vs* success, failure, or relapse (≥5)						
0–1 drugs	NA	336/1864	..	1 (ref)	..	..
2 drugs	NA	280/2087	2087	0·7 (0·6–0·8)	6·0%	–0·04 (–0·06 to –0·02)
3 drugs	NA	366/2543	2543	0·8 (0·7–0·9)	6·1%	–0·02 (–0·04 to 0·00)
4 drugs	NA	114/1211	1211	0·5 (0·4–0·6)†	4·3%	–0·10 (–0·12 to –0·08)†
>5 drugs	NA	53/529	529	0·5 (0·4–0·7)†	3·9%	–0·12 (–0·15 to –0·08)†

Results were adjusted as described in Methods. We excluded 2763 patients from the initial phase analyses (1938 patients were lost to follow-up, 825 patients were missing information about initial phase drugs) and 3796 patients from the continuation phase analyses (1938 patients were lost to follow-up, 1858 patients were missing information about continuation phase drugs). OR=adjusted odds ratio. RD=adjusted risk difference. NA=not applicable. NC=not calculated. *40 patients received seven drugs. †Significantly better outcomes than another interval, in turn significantly better than reference group.

Table 5: **Association of number of possibly effective drugs with success or death**

might have resulted in confounding of the use of certain drugs with clinical characteristics. For example, the poor treatment outcomes associated with use of capreomycin could have resulted from selective use in patients with worse clinical characteristics. However, this explanation seems less likely because 77% of patients receiving capreomycin were treated in centres where this was the most frequently used second-line injectable drug. Efficacy of linezolid might have been overestimated because it was used more often in high-income countries, whereas kanamycin was predominantly used in low-resource settings. However, overestimation was not an issue for bedaquiline, since more than 80% of patients who received bedaquiline were treated in low-middle income countries, nor capreomycin, since only 271 (9%) of capreomycin recipients were treated in low-income countries (data not shown). Comparisons were potentially biased by the fact that certain drugs we analysed were used only at a limited number of centres; because of concerns that patients who received these drugs at these centres were highly selected, we used controls from centres where these drugs were not used at all. However, this approach might have resulted in an opposite bias, if the centres using these drugs also had poorer outcomes.

The duration analyses were particularly prone to bias, because duration might have been truncated or prolonged on the basis of clinical response, and the numbers of patients included in each analysis was reduced because of missing information—particularly for the duration post-conversion analyses. We could not analyse acquired drug resistance because this was reported in too few studies, nor adverse events because of wide variability in methods of investigation, management, and reporting. Inferences for the carbapenems are also limited by small numbers of patients and studies. The effect of drug doses could not be analysed because most centres followed standard dosing recommendations, resulting in little variability. Effects of individual drugs might have been underestimated

	Success (n)	Total (N)	Propensity score matched multivariate regression			
			Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
Duration of initial phase (months)*						
0·5–5·0	1169	1432	..	1 (ref)	..	..
5·01–6·0	1381	1529	1529	1·7 (1·4–2·1)	NC	0·06 (0·04 to 0·08)
6·01–8·0	1602	1696	1695	3·2 (2·5–4·0)	NC	0·09 (0·07 to 0·10)
8·01–12·0	1346	1522	1519	1·4 (1·2–1·7)	NC	0·05 (0·03 to 0·06)
12·01–25·3	557	679	677	0·8 (0·7–1·0)	NC	–0·04 (–0·07 to –0·01)
Interval from culture conversion to end of initial phase (months)†						
0–1·0	239	251	..	1 (ref)	..	..
1·01–3·0	668	695	694	1·5 (1·0–2·3)	NC	0·02 (0·00 to 0·03)
3·01–5·0	878	917	906	1·4 (1·0–2·0)	NC	0·02 (0·00 to 0·03)
5·01–7·0	1158	1179	1179	3·3 (2·1–5·2)	NC	0·04 (0·03 to 0·05)
7·01–15·0	1025	1080	1079	1·1 (0·8–1·5)	NC	0·01 (–0·01 to 0·02)
Total duration of treatment (months)‡						
6·0–11·9	119	176	174	0·6 (0·4–0·8)	42·2%	–0·10 (–0·17 to –0·03)
12·0–16·0	250	297	..	1 (ref)	..	..
16·01–18·0	1349	1482	1482	2·8 (2·3–3·4)	11·6%	0·20 (0·18 to 0·22)
18·01–20·0	1219	1264	1264	7·5 (5·5–10·1)	10·6%	0·23 (0·22 to 0·24)
20·01–22·0	995	1091	1091	2·9 (2·3–3·6)	11·1%	0·19 (0·17 to 0·20)
22·01–24·0	1609	1911	1911	1·5 (1·3–1·7)	13·7%	0·14 (0·12 to 0·17)
24·01–36·9	1391	1611	1608	1·8 (1·5–2·0)	17·7%	0·16 (0·14 to 0·18)
Interval from sputum culture conversion to end of treatment (months)§						
0·1–12·0	360	396	394	0·5 (0·4–0·7)	NC	–0·04 (–0·07 to –0·01)
12·01–15·0	565	593	..	1 (ref)	..	..
15·01–18·0	1206	1235	1223	2·1 (1·4–3·1)	NC	0·02 (0·01 to 0·04)
18·01–21·0	1122	1158	1154	1·6 (1·1–2·3)	NC	0·02 (0·00 to 0·03)
21·01–24·0	858	893	889	1·2 (0·9–1·8)	NC	0·01 (–0·01 to 0·02)
24·01–69	386	416	413	0·7 (0·4–1·0)	NC	–0·02 (–0·05 to 0·00)

All duration analyses were restricted to the patients with treatment success or failure or relapse; the 3667 patients who died or were lost were excluded. Patients who were included or excluded in each analysis are detailed in the footnotes. OR=adjusted odds ratio. RD=adjusted risk difference. NC=not calculated. *6858 patients were included and 1505 patients were excluded (n=1323 not reported; n=182 initial phase > 25·3 months [>2 SDs from the mean]). †4122 patients included and 4241 excluded (n=3777 time to culture conversion or initial phase duration was not reported; n=390 conversion occurred after end of initial phase; n=74 sputum conversion occurred after 14·3 months [>2 SD]). ‡7832 patients included and 531 patients excluded (n=248 missing information; n=203 total duration <6 months; n=80 total duration >36·9 months [>2 SD]). §4691 patients included and 3672 excluded (n=3413 information about time to conversion or total duration missing; n=259 total duration <6 months, >36·9 months [>2 SD], or culture conversion was more than 14·3 months).

Table 6: **Association of treatment duration with treatment success**

because patients were considered as being exposed to each drug if it was taken for a month or more. Analysis within subgroups of interest, such as children, pregnant women, people with only extra-pulmonary disease, or people with diabetes was precluded by limited numbers. Finally, a high proportion of individuals were lost to follow-up during treatment, which might bias estimates of effects.

Nevertheless, this study had several strengths. Patients with widely varying severity of disease and additional resistance were treated in settings with very different practices and available resources, enhancing generalisability. Although almost all studies were observational, quality was judged as being high in 39 studies, and low in only two studies. The availability of information for many clinical characteristics allowed adjustment for potentially confounding differences using propensity score matching, considered to be a robust statistical method for observational studies.[19] Availability of drug susceptibility test results in most patients allowed assessment of the efficacy of each drug among patients with susceptible or resistant isolates.

The study has several key implications, including the consistent finding of better outcomes with use of drugs in patients with susceptible isolates, compared with resistant isolates to those drugs. This finding emphasises the value of drug susceptibility test results to guide regimen selection, and the urgent need for expansion of laboratory capacity to perform these drug susceptibility tests. The high mortality among HIV-positive patients, of whom only half had received antiretroviral therapy, is a stark reminder of the need to treat the HIV co-infection as well as the multi-drug-resistant tuberculosis. Our findings call into

question current multidrug resistance treatment recommendations to give certain drugs, such as pyrazinamide, despite in-vitro resistance. Second-line injectable drugs do not seem to be equal; amikacin was associated with better outcomes than were kanamycin or capreomycin, even in patients with extensive drug resistance, which might reflect recently described differences in pharmacokinetics between these drugs.[78]

The substantial benefit of linezolid, bedaquiline, and carbapenems, even in patients with extensive drug resistance, was not seen in our previous individual patient data meta-analysis,[4] because too few patients received these drugs in that study. Use of these new drugs, and greater use of later generation fluoroquinolones, could have contributed to the higher overall pooled success rate in this study (65%), compared with 54% in the previous meta-analysis[4] and the 2017 WHO report.[1] Our findings support immediate efforts to enhance access to these drugs, which currently is limited, despite WHO guidelines recommending wider use.[2,79,80]

A surprising finding was the lack of benefit of several commonly prescribed drugs to treat multidrug-resistant tuberculosis, including kanamycin, capreomycin, and ethionamide, by contrast with previous reports.[4] The difference might reflect the modest activity of these drugs, so they appeared beneficial in past studies when compared with weaker drugs and regimens. The limited benefits of the injectable drugs (other than carbapenems) support the need for trials to assess all-oral multidrug-resistant tuberculosis regimens with the new and repurposed drugs. Finally, the negative outcomes associated with use of macrolides and amoxicillin-clavulanic acid should guide clinicians and control programmes to avoid these drugs (except when amoxicillin-clavulanic acid is used as a companion drug with carbapenems).

This meta-analysis of individual patient data highlights the importance of selection of drugs on the basis of drug susceptibility test results, and provides useful information regarding the potential benefit of linezolid, bedaquiline, clofazimine, later generation fluoroquinolones, and the carbapenems. These results should motivate immediate and vigorous efforts to conduct randomised trials, as well as high quality observational studies, to adequately assess these drugs, and parallel efforts to expand access to them. Our findings also suggest that many of the drugs currently used for multidrug-resistant tuberculosis treatment—notably capreomycin, kanamycin, ethionamide, or protionamide, and para-aminosalicylic acid—are of uncertain benefit and their use should be reassessed.

Contributors

DM, PN, BS, GBM, and SM designed the study and protocol. NA, SDA, OWA, J-WCA, LFA, PB, DBa, PMB, MLB, DBe, GPB, MJB, MB, SKB, JCMB, YC, GFF, EC, JPC, RC, P-CC, EDC, K-CC, MC, AC, MPD, LD'A, GdV, KD, AE, JF, GF, RG, MG, MTG, SG, LG, THH, JH, PI, MF-J, LJ, RRK, SK, MK, SPK, W-JK, AK, LK, CLK, NK, CL, RL-L, ML, VL, C-CL, EC-CL, PZL, ELM, SMM, LM, GBM, VM, ACM, CDM, CM, EM, IM, NN, MRO'D, NP, DP, JWP, LJP, IR, VR, JR, MR, KJS, KS, TSS, RS, SES, GSo, GSu, PT, ST, AT, LT, ZFU, TSvdW, NV, PV, SCV, KW, JW, W-WY, J-JY, NMZ, and MZ contributed data to the meta-analysis. ZL, DM, PL, AB, and FAK did the data analysis. DM wrote the initial draft of the manuscript, and all authors provided critical input and revisions to the draft manuscripts, and approved the final manuscript.

Declaration of interests

W-JK reports consultation fees from Insmed Inc for work on the Insmed Advisory Board. CL reports receiving personal fees from Chiesi, Gilead, Janssen, Lucane, Novartis, Thermofisher, and Transgene. JR reports a grant from Janssen Pharmaceuticals. NV reports grants from Otsuka, and Janssen Pharmaceuticals. W-WY reports consultation fees from Otsuka Pharmaceutical Co. All this work was declared by the authors to be outside the submitted work. All other authors declare no competing interests.

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