




Group 5 drugs for multidrug-resistant tuberculosis: individual patient data meta-analysis

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ABSTRACT The role of so-called “group 5” second-line drugs as a part of antibiotic therapy for multidrug-resistant tuberculosis (MDR-TB) is widely debated. We performed an individual patient data meta-analysis to evaluate the effectiveness of several group 5 drugs including amoxicillin/clavulanic acid, thioacetazone, the macrolide antibiotics, linezolid, clofazimine and terizidone for treatment of patients with MDR-TB.

Detailed individual patient data were obtained from 31 published cohort studies of MDR-TB therapy. Pooled treatment outcomes for each group 5 drug were calculated using a random effects meta-analysis. Primary analyses compared treatment success to a combined outcome of failure, relapse or death.

Among 9282 included patients, 2191 received at least one group 5 drug. We found no improvement in treatment success among patients taking clofazimine, amoxicillin/clavulanic acid or macrolide antibiotics, despite applying a number of statistical approaches to control confounding. Thioacetazone was associated with increased treatment success (OR 2.6, 95% CI 1.1–6.1) when matched controls were selected from studies in which the group 5 drugs were not used at all, although this result was heavily influenced by a single study.

The development of more effective antibiotics to treat drug-resistant TB remains an urgent priority.

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Introduction

Multidrug-resistant tuberculosis (MDR-TB) represents a substantial global public health challenge, affecting half a million people each year worldwide [1]. Among the minority of MDR-TB patients who are correctly diagnosed, only 50% are successfully treated and 16% die during treatment [1, 2]. MDR-TB is resistant to the two most effective first-line antibiotics, isoniazid and rifampicin, while extensively drug-resistant (XDR)-TB is also resistant to the most effective second-line drugs (fluoroquinolone antibiotics and second-line injectables (SLIs)). World Health Organization guidelines recommend that at least four effective second-line antituberculosis drugs (as well as pyrazinamide) be combined in the intensive phase of treatment [3]. Second-line drugs are divided into four groups: SLIs, fluoroquinolones, oral bacteriostatic agents (“group 4” drugs) and “group 5” drugs (G5Ds). We considered linezolid, amoxicillin/clavulanate, thioacetazone, clarithromycin, imipenem and terizidone to be G5Ds [2]. These drugs constitute a heterogeneous group of antibiotics with different structures and mechanisms of action [3]. Substantial debate has surrounded the role of these antibiotics as therapy for drug-resistant TB [4], given their potential toxicities and limited evidence of clinical effectiveness for most [5, 6]. Animal studies suggest that some G5Ds may improve treatment outcomes, when used in combination with standard therapies [7]. Two randomised studies have shown improved treatment outcomes with linezolid in XDR-TB (but not MDR-TB) [8, 9]. A randomised study of clofazimine has been published [10], although the study was not blinded, and the participation rate was not stated, potentially introducing bias. However, recommendations regarding most G5Ds rely upon observational data. While observational studies have shown promising results with some G5Ds, treatment allocation was not randomised in most studies and hence highly prone to selective treatment allocation. Three previously published meta-analyses evaluating the effectiveness of clofazimine [5, 11, 12] and other G5Ds [5] have been inconclusive. Of these, two were aggregate data meta-analyses [11, 12]. Such meta-analyses have been unable to account for selection bias and confounding, lacking data about the characteristics of individual patients, which may have affected treatment assignment. In contrast, individual patient data (IPD) meta-analyses are considered the gold standard for combining data from multiple studies [13]. This approach is better able to account for heterogeneity in treatment allocation [14], which is a particularly important issue for analysing regimens such as those used for MDR-TB. Therefore, we aimed to evaluate the effectiveness of G5Ds (treatment success *versus* death, failure or relapse) using individual patient data from published cohort studies of patients treated for bacteriologically confirmed MDR-TB.

Methods

Study selection

Studies were eligible for inclusion if they were included in one of three published aggregate data meta-analyses of MDR-TB treatment (online supplementary table S1) [15–17] and included ≥ 25 patients with MDR-TB. Authors of eligible cohort studies were invited to contribute individual patient datasets. Studies were included if authors agreed to submit the individual patient datasets for their published studies. Aggregate data from studies that did not provide individual patient data were excluded. Other aspects of study selection have been described previously [2]. Of the 32 studies in the original IPD meta-analysis, one was excluded from the present analyses at the request of the authors [18]. The individual patient datasets included participant demographics, clinical markers of disease severity (smear status, cavitation on chest radiograph and bilateral disease), phenotypic drug susceptibility of cultured isolates and detailed medical regimens. Treatment outcomes were defined according to published standard definitions, and included success (comprising cure or treatment completion), death, relapse, treatment failure or loss to follow-up (default) [19].

Individual patient selection

Patients from the 31 included studies for whom data were available were excluded if they had only extrapulmonary disease but not pulmonary disease or if treatment information was unavailable. Individuals for which details of the antibiotic regimen was unavailable were also excluded.

Definitions

All included patients had confirmed MDR-TB, with or without resistance to additional antibiotics, as defined by culture and phenotypic drug susceptibility testing [20]. Patients living with HIV infection were included. Primary treatment outcomes (treatment success, failure, death, relapse and loss to follow-up) were defined according to criteria proposed by LASERSON *et al.* [19].

Exposed patients were those taking one of the G5Ds of interest (amoxicillin/clavulanic acid, clofazimine, linezolid, terizidone, thioacetazone, clarithromycin or imipenem) at any time during their therapy, while unexposed patients were not given that drug. In analyses of the individual drugs, unexposed subjects may have taken another G5D.

Data were obtained relating to the clinical characteristics of patients, treatment regimens and treatment outcomes. Data were checked for consistency and completeness prior to analysis, using statistical software (Proc Univariate, SAS version 9.3; SAS Institute, Cary, NC, USA; <https://support.sas.com/documentation/93/index.html>).

Descriptive analysis

Simple descriptive statistics were used to compare the characteristics of patients receiving each G5D, and those not receiving the drug. Pooled treatment outcomes for each G5D and for those patients receiving one or more G5Ds, were calculated using a one-step meta-analysis. Study-level heterogeneity in the univariable analyses was reported using the I^2 statistic and its 95% confidence intervals as described by HIGGINS *et al.* [21].

Analytic model

For each G5D that was taken by ≥ 40 individuals, a one-stage meta-analysis was performed using a random effects logistic regression model to evaluate, for each drug, the odds of treatment success (defined as cure or completion) against a combined outcome of treatment failure, relapse and death. A secondary analysis was performed in comparing the odds of treatment success against failure, relapse, death and loss to follow-up (default).

For each G5D the primary comparison was between exposed and unexposed patients in studies where that G5D was available: patients receiving G5Ds (group G5) *versus* patients not receiving group 5 drugs (group NG5a). In order to account for possible selection bias, a secondary comparison was performed for exposed patients in studies where each G5D was available (group G5) and compared with unexposed patients in studies where that group G5D not available (group NG5b). The latter comparison was used to overcome confounding by indication, since patients in the NG5b group (from a centre where no G5Ds were used) could not be given a G5D regardless of their clinical and treatment characteristics. The rationale for this approach has been described [22].

Unadjusted (crude) and adjusted analyses were performed. Two methods were used to adjust for potential confounding. The rationale for using several alternative analytic methods to account for confounding by indication has been described [22]. First, a traditional hierarchical multivariable logistic regression model was fitted. This aimed to adjust for important baseline characteristics and treatment characteristics likely to influence patient outcomes, including the following covariates: sex, age, disease extent (defined as extensive if the disease was either sputum smear acid-fast bacillus-positive or cavitation was seen on chest radiography), prior treatment with first- or second-line drugs, the number of drugs in the intensive phase and the total duration of antibiotic therapy. These were chosen based upon a directed acyclic graph including possible sources of confounding.

In addition, a second adjustment method used propensity score-based matching to account for differences in baseline characteristics and treatment regimens. This method aimed to address potential confounding by indication, if patients were allocated to treatment on the basis of their clinical characteristics. Application of propensity scores to IPD meta-analysis has been described recently [22]. Propensity scores are an estimate of the probability that a patient with a given set of covariates will be allocated to the exposure (a G5D), and may be used to account for confounding (including confounding by indication) in a regression analysis [23]. Propensity scores were estimated for each individual patient using standard logistic regression, including the following covariates: sex, age, extent of disease, prior TB, prior MDR-TB, number of drugs in the intensive phase and total duration of therapy. Propensity scores were allocated separately according to the selected comparison: 1) within studies where a specific G5D was available (comparing patients taking that G5Ds with those not taking that G5D) or 2) between subjects taking a specific G5D *versus* subjects in studies where that G5D was unavailable. Each exposed individual was matched with one unexposed individual, where a suitable match could be found. After each selection, unexposed subjects were returned to the pool of subjects and were eligible for repeat selection (*i.e.* one-to-one matching with replacement). The matching algorithm used nearest-neighbour matching to identify pairs of treated and untreated subjects [24].

The effectiveness of covariate balance achieved by matching was evaluated by calculating the standardised difference of the covariates, and logit of the propensity score, between exposed and unexposed groups [25–27]. Differences between treatment groups of $<10\%$ for individual covariates implied balance in these potential confounders [28]. Heterogeneity between studies was assessed by calculating I_R^2 from the standard error of the random effects and fixed-effects models [29].

Study, treatment and match were random effects in the propensity score models. This provided adjusted odds of treatment success for patients who used G5Ds. Patients were clustered at the level of the study and intercepts and slopes varied across studies. If models did not converge, the covariance requirement between slope and intercept was removed. If convergence still did not occur, then the random intercept

was removed. If a fixed-effects model was required, this was reported. The models were estimated *via* penalised quasi-likelihood (Proc Glimmix, SAS 9.3).

Missing covariate values in the individual patient dataset were imputed using multiple imputation (Proc MI, SAS 9.3), propensity scores were estimated and then patients with and without the drug were matched based upon propensity score. Analyses were performed in SAS (9.3).

The study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for individual patient data meta-analysis [30]. The authors did not prepare a formal written study protocol. The analytic approach has been described previously [22].

Results

Individual patient data for 9282 patients was obtained from the authors of 31 studies; in 24 of these studies at least one patient received at least one G5D (figure 1). In these studies, 2191 individuals took regimens containing at least one G5D (table 1). The remaining seven studies where no G5Ds were given included 2875 individuals. 919 patients were given amoxicillin/clavulanic acid, 806 clofazimine, 532 clarithromycin, 705 thioacetazone, 32 terizidone, nine imipenem and 39 linezolid.

Online supplementary table S2 summarises the settings and treatment regimen used in each included study. Online supplementary table S3 shows the number of patients taking G5Ds for each included study. Online supplementary table S4 shows the proportion of non-missing data for each independent variable included in the multivariable regression, grouped according to individual studies. The table also shows the proportion of individuals lost to follow-up in each study. No important issues were identified in checking the individual patient data.

The median (interquartile range) treatment duration for patients taking a G5D was 20.9 (14.6–25.6) months compared to 14.4 (6.3–20.0) months for those not taking a G5D ($p < 0.01$). 50.8% of patients taking a G5D had MDR-TB with additional resistance to either fluoroquinolones or injectable antibiotics or both, compared with only 33.1% of patients not taking a G5D. Most patients taking a G5D were taking only one (67.9%) or two (26.6%) G5Ds.

Table 2 shows the pooled treatment outcomes, according to which G5D was taken. When excluding subjects lost to follow-up, 74% of subjects taking a G5D were treated successfully, compared to 73% of those not taking a G5D. The proportion with treatment success was similar if patients lost to follow-up were included (61% *versus* 58%).

The proportion lost to follow-up varied considerably; only 8% (95% CI 4–11%) of those taking clofazimine and 6 (3–10)% of those taking amoxicillin/clavulanic acid were lost to follow-up, compared to 20% of those not taking any G5Ds.

Among patients taking clofazimine, patients with smear-positive disease, pre-XDR disease or extrapulmonary TB had reduced treatment success, after adjustment (table 3). Those with an overall longer duration of treatment, or taking at least four effective drugs had an increased odds of success, after adjustment.

Propensity score matching improved the covariate balance between most covariates of individuals with and without G5Ds (table 4). Before matching, standardised difference of the logit of the propensity score was 40.7% lower among those taking clofazimine compared to those not taking clofazimine, while this was only 0.1% lower after one-to-one matching with replacement (implying almost perfect covariate balance).

Table 5 shows the relationship between the use of each G5D, where data from ≥ 50 patients were available, and treatment success (compared to death, failure or relapse) using multivariable analysis or propensity score-based matching. When control subjects were obtained only from studies where G5Ds were used (group G5 *versus* NG5a), adjusted (multivariable) estimates found that treatment success was lower among those taking clofazimine, amoxicillin/clavulanic acid and clarithromycin. After matching, clofazimine, amoxicillin and thioacetazone were no longer associated with reduced treatment success. When controls were selected only from studies where G5D were not used, no benefit was found with use of any G5D.

Table 6 also includes subjects lost to follow-up, comparing treatment success to death, failure relapse and loss to follow-up. Only thioacetazone was associated with increased treatment success (OR 2.6, 95% CI 1.1–6.1) in the matched analyses when controls were taken from studies where a G5D was not used by any patients (G5D *versus* NG5b). However, 95% of the 705 patients treated were thioacetazone were from a single study site (online supplementary table S5) [32]. Heterogeneity in the matched analysis was moderate, with I^2 estimates of $< 40\%$ seen for most comparisons.

Online supplementary table S6 shows the PRISMA-IPD checklist of items according to be included when reporting an IPD meta-analysis. Individual study quality was not formally assessed. Online supplementary table S7 provides a risk of bias assessment for the included studies.

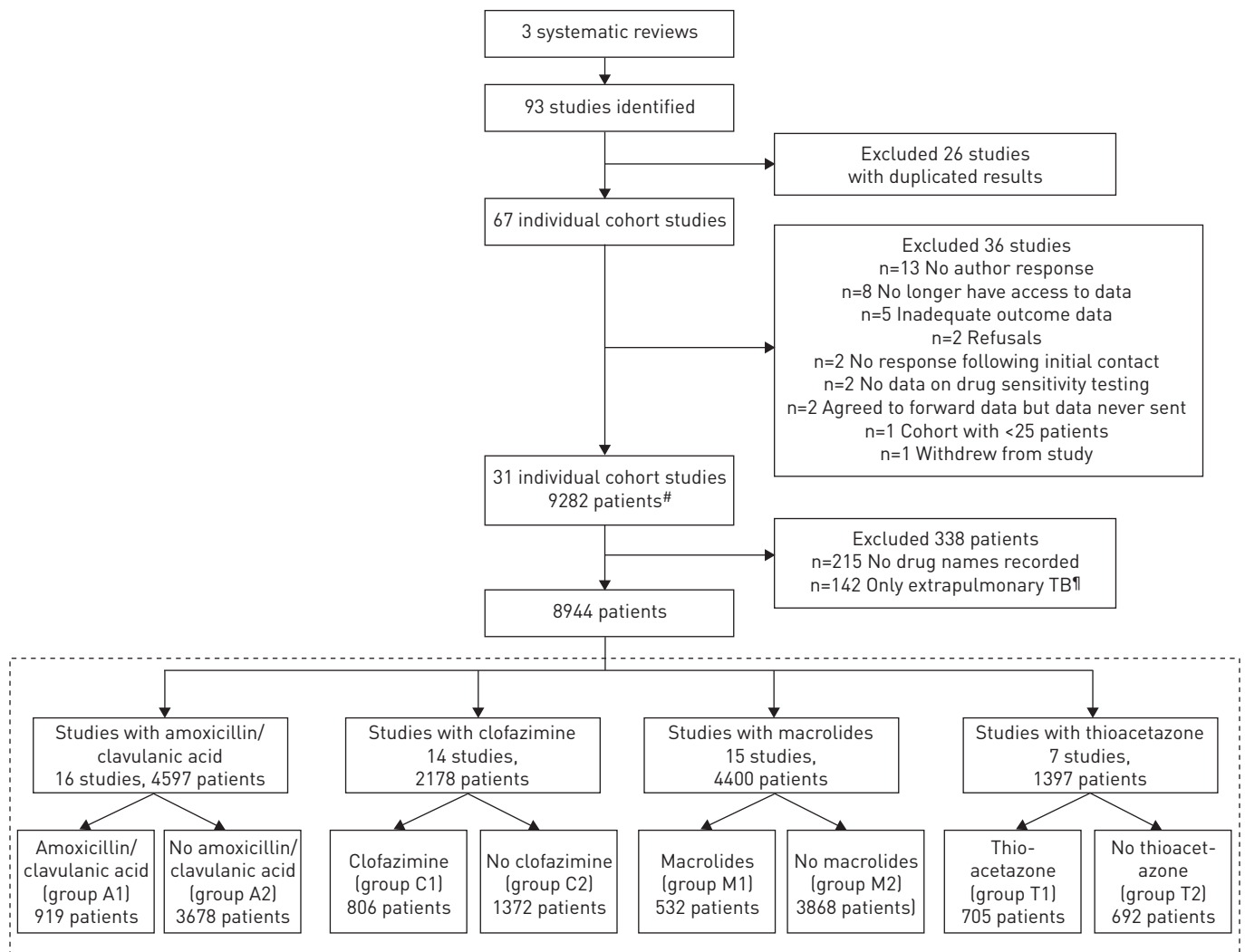


FIGURE 1 Consort diagram for individual patient data meta-analysis of group 5 drugs for multidrug-resistant tuberculosis (TB). Among studies included in the present meta-analyses, 2191 patients from 24 studies took at least one group 5 drug: amoxicillin/clavulanic acid (n=919 patients, 16 studies), clofazimine (n=806 patients, 14 studies), macrolide antibiotics (n=532 patients, 15 studies), thioacetazone (n=705 patients, seven studies), linezolid (n=39 patients, four studies), imipenem (n=7 patients, four studies) and teridizone (n=12 patients, one study). #: Patients from 31 cohort studies were included in these analyses. The authors of one study included in the previously published meta-analysis withdrew from the present study [2]; †: 19 excluded patients had both extrapulmonary TB and no drug names recorded.

Discussion

This IPD meta-analysis of 31 studies evaluated the effect of four G5Ds among 2191 patients treated for MDR-TB. We found improvement in treatment outcomes among patients treated with thioacetazone but not among patients who received clofazimine, amoxicillin/clavulanic acid or macrolide antibiotics. Our findings support a conservative approach to using these G5Ds, and suggest that alternative drugs should be used where possible [33].

An interesting finding of this study was improved treatment outcomes among patients taking thioacetazone, when patients in studies taking the drug were compared to patients in studies where the drug was not used. This result predominantly arose from one study from Latvia, which contributed 95% of the 705 patients who received thioacetazone [32], and achieved a higher treatment success rate among those taking thioacetazone than was seen in other studies. This may reflect, in part, the overall strength of treatment in that setting, where the majority of patients received thioacetazone. Hence, while the finding may reflect a true benefit of the drug, study-specific factors related to patient selection for thioacetazone or differences in the patient populations may also be responsible. The absence of an effect when patients within the same study were used as controls points towards possible confounding by indication, as we have discussed previously [22]. Therefore, this finding should be interpreted with caution.

TABLE 1 Participant characteristics, classified by whether at least one group 5 drug was used

	Studies in which at least some patients received group 5 drugs			Studies in which no patients received any group 5 drugs	
	Patients taking any group 5 drug (group G5)	Patients not taking any group 5 drugs (group NG5a)	p-value (G5 versus NG5a)	Patients not taking any group 5 drugs (group NG5b)	p-value (G5 versus NG5b)
Subjects	2191	3878			
Male	1474 (67.3)	2766 (71.3)	<0.01	1865 (64.9)	0.08
Age years	37.8±13.1	40.6±14.5	<0.01	38.2±12.5	0.35
Disease characteristics					
Smear positive	1202 (76.1)	2495 (73.6)	0.06	1988 (75.2)	0.53
Extensive disease [#]	1607 (74.8)	2764 (72.1)	0.02	2103 (75.5)	0.59
Bilateral disease	123 (61.5)	1024 (71.5)	<0.01	NA	NA
Cavitary disease	1403 (79.3)	1723 (55.4)	<0.01	1412 (80)	0.59
HIV infection	81 (4.1)	439 (12.0)	<0.01	571 (27.9)	<0.01
Antibiotics n					
Intensive phase	6 (5–7)	5 (4–6)	<0.01	5 (5–5)	<0.01
Continuation phase	5 (4–6)	4 (3–4)	<0.01	3 (3–3)	<0.01
Months of therapy n					
Total	20.9 (14.6–25.6)	14.4 (6.3–20.0)	<0.01	18 (17.6–18.0)	<0.01
Intensive phase	9 (6–9)	7 (4–9)	<0.01	3 (3–3)	<0.01
Continuation phase	10.1 (0.3–15.7)	3.6 (0–11.9)	<0.01	15 (15–15)	<0.01
Degree of antibiotic resistance					
MDR [¶] only	798 (49.2)	2033 (66.9)	<0.01	1945 (93.9)	<0.01
MDR and quinolone resistance	152 (9.4)	243 (8)	0.11	29 (1.4)	<0.01
MDR and injectable resistance	499 (30.8)	575 (18.9)	<0.01		<0.01
XDR [*]	173 (10.7)	190 (6.2)	<0.01	42 (2)	<0.01
Antibiotics used					
Group 5 drugs					
Amoxicillin/clavulanic acid	919 (42.3)				
Clofazimine	806 (38.7)				
Linezolid	39 (2.5)				
Thioacetazone	705 (34.0)				
Clarithromycin	532 (24.3)				
Terizidone	32 (1.5)				
Imipenem	7 (0.5)				
Combinations of group 5 drugs					
Any 1	1487 (67.9)				
Any 2	582 (26.6)				
Any 3	119 (5.4)				
Any 4	3 (0.1)				

Data are presented as n, n (%), mean±SD or median (interquartile range), unless otherwise stated. Group 5 drugs are defined as amoxicillin/clavulanic acid, clofazimine, linezolid, clarithromycin or imipenem. MDR: multidrug-resistant; XDR: extensively drug-resistant; NA: not applicable. [#]: defined as a combination of smear positive and cavitary disease; [¶]: defined as resistant to isoniazid and rifampicin; ^{*}: defined as MDR plus resistance to an injectable second-line antibiotic and a fluoroquinolone.

We found no benefit with clofazimine using any of our analytic approaches, consistent with a previous meta-analysis including 42 patients taking the drug [5]. This contrasts with a recent randomised controlled trial from China (53 patients taking clofazimine, 52 patients not taking clofazimine) which found a substantial increase in treatment success with clofazimine in MDR-TB [10]. Although the effect estimate was not reported, using the study data we calculated the odds ratio for treatment success with clofazimine in the Chinese study to be 2.4 (95% CI 1.6–3.2), when compared to those not taking the drug. Importantly, the study was not blinded, and the participation rate was not stated, potentially introducing bias. Another recent cohort study also found improved outcomes with clofazimine for treating XDR-TB [34], and animal studies have shown evidence of faster time to cure using the drug [7]. The explanation for this difference between our meta-analysis and these published studies remains unclear. It is possible that the lack of blinding could have introduced bias in the Chinese study, and confounding by indication may have biased the South African [34] study, although these findings clearly warrant further investigation. In the animal study, use of three active drugs (rather than the usual two) during the continuation phase may have contributed to the greater effectiveness of the clofazimine-containing regimen. Nonetheless, given the observational nature of the cohort studies included in our meta-analysis,

TABLE 2 Pooled treatment outcomes according to group 5 drug use, among studies where the drug was used

	Events	Total	Pooled treatment outcomes [#]	Measures of heterogeneity	
				I ²	τ ²
Outcomes excluding loss to follow-up					
Treatment success [¶]					
No group 5 drugs	1835	2762	75 (65–81)	98 (97–98)	0.059
At least one group 5 drug	1357	1894	74 (66–81)	94 (92–95)	0.032
Clarithromycin	287	457	74 (68–80)	45 (0–70)	0.006
Clofazimine	459	699	74 (59–90)	96 (95–97)	0.079
Amoxicillin/clavulanic acid	545	809	84 (80–87)	29 (0–61)	0.003
Thioacetazone	491	612	80 (77–83)	0 (0–71)	0.000
Terizidone	13	16	76 (51–100)	0 (0–85)	0.000
Linezolid	12	22	50 (28–71)	0 (0–90)	0.000
Outcomes including loss to follow-up					
Treatment success [¶]					
No group 5 drugs	1835	3878	60 (50–70)	98 (97–98)	0.055
At least one group 5 drug	1357	2191	61 (53–69)	92 (90–94)	0.031
Clarithromycin	287	532	58 (51–66)	65 (39–80)	0.013
Clofazimine	459	806	63 (49–78)	95 (93–96)	0.071
Amoxicillin/clavulanic acid	545	919	68 (62–73)	53 (18–73)	0.007
Thioacetazone	491	705	70 (66–73)	0 (0–71)	0.000
Terizidone	13	32	30 (14–46)	0 (0–85)	0.000
Linezolid	12	39	28 (13–42)	0 (0–85)	0.000
Treatment failure or relapse					
No group 5 drugs	255	3878	3 (2–4)	50 (18–69)	0.000
At least one group 5 drug	253	2191	9 (6–12)	83 (75–88)	0.005
Clarithromycin	97	532	10 (6–14)	49 (7–72)	0.004
Clofazimine	48	806	2 (0–4)	32 (0–64)	0.001
Amoxicillin/clavulanic acid	108	919	13 (6–20)	82 (71–88)	0.016
Thioacetazone	97	705	14 (11–16)	0 (0–71)	0.000
Terizidone	2	32	20 (0–45)	0 (0–85)	0.000
Linezolid	1	39	33 (0–87)	0 (0–85)	0.000
Loss to follow-up					
No group 5 drugs	1116	3878	20 (12–27)	96 (96–97)	0.029
At least one group 5 drug	297	2191	11 (7–14)	80 (72–86)	0.005
Clarithromycin	75	532	12 (7–18)	68 (44–81)	0.007
Clofazimine	107	806	8 (4–11)	55 (19–76)	0.003
Amoxicillin/clavulanic acid	110	919	6 (3–10)	66 (43–80)	0.004
Thioacetazone	93	705	13 (11–16)	0 (0–71)	0.000
Terizidone	16	32	22 (1–44)	46 (0–82)	0.041
Linezolid	17	39	48 (31–66)	0 (0–85)	0.000
Death					
No group 5 drugs	672	3878	11 (5–17)	97 (97–98)	0.021
At least one group 5 drug	284	2191	10 (6–15)	91 (87–93)	0.012
Clarithromycin	73	532	8 (3–13)	75 (58–85)	0.007
Clofazimine	192	806	14 (5–24)	86 (77–91)	0.030
Amoxicillin/clavulanic acid	156	919	6 (2–9)	60 (30–77)	0.004
Thioacetazone	93	705	13 (11–16)	0 (0–71)	0.000
Terizidone	1	32	6 (0–16)	0 (0–85)	0.000
Linezolid	9	39	25 (11–39)	0 (0–85)	0.000

Data are presented as n or % [95% CI], unless otherwise stated. τ²: the estimated standard deviation of underlying effects across the studies. #: weighted treatment outcomes [31]; ¶: defined as cure or treatment completion.

we cannot exclude the possibility that unmeasured confounding resulted in an underestimate of the effect of clofazimine. Hence, our results suggest that additional data from well-designed and -executed randomised trials are still warranted, before widely adopting clofazimine as initial therapy for MDR-TB.

Estimates for the effect of treatment differed depending upon the population from which control subjects were selected. When control subjects (*i.e.* those not taking a given G5D) were selected from studies where the G5D was available, three drugs (clofazimine, amoxicillin/clavulanic acid and macrolide antibiotics) demonstrated reduced treatment success, but, when controls were drawn from studies where the drug was not available, there was no apparent effect of the drug at all. This finding points toward a potential

TABLE 3 Univariable analysis of treatment success *versus* death or treatment failure among patients taking clofazimine

	Subjects [#]	Univariable analysis	Multivariable analysis [¶]	Measures of heterogeneity	
				R statistic	I ² _k
Subjects n	699				
Subject characteristics					
Age [*]	699	0.9 (0.8–1.0)	0.9 (0.8–1.1)	1.038	0.037
Male	699	1.1 (0.8–1.6)	1.2 (0.8–1.7)	1.017	0.017
Disease characteristics					
Cavitation on radiography (<i>versus</i> no cavitation)	459	0.6 (0.3–1.2)	0.5 (0.2–1.0)	1.013	0.013
Smear-positive at diagnosis (<i>versus</i> not smear-positive)	634	0.3 (0.2–0.5)	0.3 (0.2–0.5)	1.009	0.008
Extensive disease [§]	699	0.3 (0.2–0.5)	0.3 (0.2–0.5)	1.015	0.015
Pre-XDR-TB (<i>versus</i> MDR-TB but not XDR-TB)	699	0.5 (0.3–0.9)	0.6 (0.3–0.9)	1.028	0.027
XDR-TB (<i>versus</i> MDR-TB, not pre-XDR-TB)	322	0.5 (0.2–1.5)	0.4 (0.1–1.2)	1.051	0.048
EPTB also present (<i>versus</i> PTB only)	699	0.2 (0.1–0.4)	0.2 (0.1–0.5)	1.004	0.003
HIV-positive (<i>versus</i> HIV-negative)	699	0.2 (0.1–0.5)	0.5 (0.1–4.3)	1.000	0.000
Medical therapy					
Total duration of therapy ^f	699	1.1 (1.1–1.2)	1.1 (1.1–1.2)	1.038	0.037
Number of antibiotics used					
Intensive phase					
<3 effective drugs		Ref.	Ref.		
4 effective drugs (<i>versus</i> <3)	71	2.1 (0.2–20.7)	1.0 (0.1–13.5)	1.036	0.068
5 effective drugs (<i>versus</i> <3)	125	1.8 (0.3–12.4)	1.5 (0.2–10.5)	1.025	0.048
6 effective drugs (<i>versus</i> <3)	197	1.7 (0.2–12.3)	0.8 (0.1–9.6)	1.017	0.033
7 effective drugs (<i>versus</i> <3)	189	0.1 (0.0–11.9)	0.3 (0.0–6.0)	1.066	0.12
8 effective drugs (<i>versus</i> <3)	93	2.3 (0.3–16.4)	0.1 (0.0–1.3)	1.000	0.000
Continuation phase					
<3 effective drugs		Ref.	Ref.		
≥3 effective drugs (<i>versus</i> <3)	95	2.6 (0.8–8.5)	2.7 (0.7–10.7)	1.020	0.040
≥4 effective drugs (<i>versus</i> <3)	144	2.6 (1.0–6.6)	3.2 (1.2–8.8)	1.016	0.031
≥5 effective drugs (<i>versus</i> <3)	368	5.0 (2.1–11.9)	5.7 (2.3–13.8)	1.017	0.032

Data are presented as n or OR (95% CI), unless otherwise stated. XDR-TB: extensively drug-resistant tuberculosis; MDR-TB: multidrug-resistant TB; EPTB: extrapulmonary TB; PTB: pulmonary TB. [#]: 422 out of 478 patients were included for the comparison treatment success *versus* failure or death; [¶]: an odds ratio of >1 indicates a higher odds of treatment success, compared to death or treatment failure; ^{*}: the odds ratio reflects the odds of treatment success for each additional decade of increased age; [§]: defined as either smear-positive TB or cavitory disease; ^f: measured in 1-month increments; the odds ratio can be interpreted as the increased odds of treatment success given each additional month of total therapy. Bold text indicates results where the 95% confidence intervals do not cross the null (OR=1.0).

residual confounding by indication, whereby the sicker patients may be systematically offered G5Ds. The use of two alternative control populations, in order to address confounding by indication, is a strength of this study, as described later.

Another intriguing finding was that rates of loss to follow-up varied considerably between patients taking some G5Ds (6% for amoxicillin/clavulanic acid and 8% for clofazimine) and patients not given any G5Ds (20% for those not taking a G5D). This could point towards possible ascertainment bias in the group not given G5Ds (*e.g.* death, failure and relapse may have been underestimated among those lost to follow-up). However, effect estimates were similar regardless of whether participants lost to follow-up were included in the analyses. This suggests that the proportion of individuals lost to follow-up was not an important contributor to treatment outcomes.

A key strength of this study was the inclusion of a large number of patients taking G5Ds across 31 studies. Although the heterogeneity in effect estimates observed between included studies might conceal small effect estimates (*i.e.* decrease the study power), by using a hierarchical model we were able to account for this variability and hence assess the independent effect of the treatment upon treatment outcomes. In contrast to our previous IPD analysis, where patients taking any other G5Ds were excluded as controls for patients taking a given G5D [2], in the present analyses we included individuals taking other G5Ds as control subjects. This approach is robust, given that the patients given other G5Ds are also likely to be more sick (*i.e.* to be failing on existing therapies). Removing all patients taking other G5Ds from our analyses may have removed the sickest individuals and introduced further bias.

TABLE 4 Matching of covariates achieved using one-to-one propensity score matching, with replacement, for clofazimine (CFZ) versus no CFZ, within studies where CFZ was used

	Patients taking CFZ	Patients not taking CFZ	Before matching (CFZ versus no CFZ)		After matching (CFZ versus no CFZ)	
			p-value	Standardised difference [#] %	p-value	Standardised difference [#] %
Male	0.62±0.49	0.65±0.48	0.162	-6.7	0.5102	1.3
Age years	34.28±12.51	38.06±14.52	<0.0001	9.85	0.207	2.4
Extensive disease	0.79±0.4	0.79±0.41	0.724	1.9	0.0014	5.9
Prior TB	0.29±0.45	0.31±0.46	0.347	-4.6	0.0171	-3.5
Prior MDR-TB	0.54±0.5	0.16±0.37	<0.0001	85.7	0.1078	1.5
HIV infection	0.1±0.3	0.36±0.48	<0.0001	-64.5	0.1066	2.7
Antibiotics used in the intensive phase	6.15±1.39	4.4±2.29	<0.0001	-32.6	0.053	-2.3
Total therapy months	22.53±11.44	16.6±12.32	<0.0001	-17.6	0.054	3.5
Logit of PS	0.13±0.99	-1.22±1.35	<0.0001	-40.7	0.039	-0.1

This table is presented as an example. This matching was performed for all group 5 drugs, for which these comparisons were performed. TB: tuberculosis; MDR-TB: multidrug-resistant TB; PS: propensity score. [#]: percentage mean difference as a percentage of the average standard deviation.

An important study limitation was the observational nature of the included cohort data. Since G5Ds have uncertain efficacy, and well-known toxicity, guidelines recommend that G5Ds should be reserved for the patients with the fewest effective treatment options [3]. This can be seen most clearly in the low rate of treatment success treated with any G5D, despite adjustment. The lower treatment success seen in the multivariable analyses probably indicates an effect of treatment allocation to more severely ill patients, rather than an adverse biological effect.

Conclusions

This individual patient data meta-analysis found that G5Ds had limited benefit in treating patients with MDR-TB. The recent availability of bedaquiline [35] and delamanid [36] has provided some new hope for patients with advanced drug resistance. Given that regimens for MDR-TB remain toxic, lengthy and complex, new drug development remains an urgent priority in global TB control.

TABLE 5 The relationship between drug use and treatment success compared to death, failure or relapse, using multivariable- and propensity score-matched analyses to adjust for potential confounding[#]

	Unadjusted estimate	Adjusted multivariable estimate [†]	Adjusted estimate using matching	Measures of heterogeneity with matched model I _R ²
G5D used (comparison is with NG5a patients from same centres)				
Clofazimine	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.6 (0.2–1.6)	0.445
Amoxicillin/clavulanic acid	0.6 (0.3–0.9)	0.4 (0.3–0.5)	0.9 (0.4–1.9)	0.337
Thioacetazone	0.9 (0.6–1.2)	0.8 (0.5–1.1)	0.8 (0.5–1.2) [*]	NA
Clarithromycin	0.5 (0.4–0.6)	0.4 (0.4–0.6)	0.6 (0.4–0.9)	0.143
G5D used (comparison is with NG5b patients from other centres)				
Clofazimine	1.0 (0.4–2.6)	1.1 (0.4–2.8)	1.4 (0.5–4.0)	0.444
Amoxicillin/clavulanic acid	0.4 (0.3–0.6)	0.4 (0.2–0.8)	0.9 (0.4–1.9)	0.303
Thioacetazone	1.8 (0.6–5.1) [*]	2.1 (0.8–5.6)	2.1 (0.8–5.5)	0.447
Clarithromycin	0.7 (0.4–1.5)	0.7 (0.3–1.3)	0.7 (0.2–1.9)	0.310

Data are presented as OR (95% CI), unless otherwise stated. The I_R² statistic quantifies the between-study variability. G5D: group 5 drug; NG5a: patients from studies where that G5D was available, but who did not receive any G5Ds; NG5b: unexposed patients in studies where that G5D was not available; NA: not applicable, as only fixed-effects model used. [#]: Linezolid and terizidone were not included in these adjusted analyses, as too few patients received these drugs; [†]: adjusting for age, sex, extent of tuberculosis (TB), prior TB, prior multidrug-resistant TB, number of drugs in the intensive phase, total duration of therapy and HIV status. Analyses include subjects within studies where at least one person used the G5D; ^{*}: hierarchical model for thioacetazone did not converge on account of substantial heterogeneity between studies, hence results from fixed-effects model are presented.

TABLE 6 The relationship between drug use and treatment success compared to death, failure, relapse or loss to follow-up, using multivariable- and propensity score-matched analyses to adjust for potential confounding[#]

	Unadjusted estimate		Adjusted multivariable estimate [†]		Adjusted estimate using matching		Measures of heterogeneity with matched model I^2
G5D used (comparison is with NG5a patients from same centres)							
Clofazimine	0.6	{0.4–0.7}	0.5	{0.4–0.7}	0.7	{0.3–1.4}	0.424
Amoxicillin/clavulanic acid	0.7	{0.6–0.9}	0.6	{0.4–0.7}	0.9	{0.5–1.5}	0.392
Thioacetazone	0.9	{0.7–1.2}	0.9	{0.6–1.3}	0.9	{0.7–1.3} [*]	NA
Clarithromycin	0.7	{0.6–0.8}	0.7	{0.6–0.9}	0.7	{0.4–1.0}	0.138
G5D used (comparison is with NG5b patients from other centres)							
Clofazimine	1.1	{0.5–2.3}	0.8	{0.4–1.9}	1.1	{0.5–2.6}	0.109
Amoxicillin/clavulanic acid	0.8	{0.4–1.3}	0.4	{0.2–0.8}	0.7	{0.3–1.5}	0.126
Thioacetazone	2.4	{0.9–6.4}	2.8	{1.0–7.3} [§]	2.6	{1.1–6.1}	0.000
Clarithromycin	0.8	{0.4–1.5}	0.7	{0.4–1.4}	0.7	{0.2–1.9}	0.330

Data are presented as OR [95% CI], unless otherwise stated. The I^2 statistic quantifies the between-study variability. G5D: group 5 drug; NG5a: patients from studies where that G5D was available, but who did not receive any G5Ds; NG5b: unexposed patients in studies where that G5D was not available; NA: not applicable, as only fixed-effects model used. [#]: Linezolid and terizidone were not included in these adjusted analyses, as too few patients received these drugs; [†]: adjusting for age, sex, extent of tuberculosis (TB), prior TB, prior multidrug-resistant TB, number of drugs in the intensive phase, total duration of therapy and HIV status. Analyses include subjects within studies where at least one person used the G5D; ^{*}: hierarchical model did not converge on account of substantial heterogeneity between studies, hence results from fixed-effects model are presented; [§]: $p=0.043$.

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