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Drug resistance beyond XDR-TB: results from a large individual patient data meta-analysis

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Summary (word count 200)

The broadest pattern of tuberculosis drug resistance for which a consensus definition exists is extensively drug-resistant tuberculosis (XDR-TB). It is not known if additional drug resistance portends worsened patient outcomes. This study compares treatment outcomes of XDR-TB patients with and without additional resistance to explore the need for a new definition.

Individual patient data on XDR-TB outcomes were included in a meta-analysis comparing outcomes between XDR-alone and three non-mutually exclusive XDR-TB patient groups: XDR plus resistance to all the second-line injectables (sli) capreomycin and kanamycin/amikacin (XDR+2sli); XDR plus resistance to second-line injectables and to ≥1 Group 4 drug, i.e.: ethionamide/prothionamide, cycloserine/terizidone or PAS (XDR+sliG4); and XDR+sliG4 plus resistance to ethambutol and/or pyrazinamide (XDR+sliG4EZ).

Of 405 XDR-TB cases, 301 were XDR-alone; 68 XDR+2sli; 48 XDR+sliG4; and 42 XDR+sliG4EZ. In multivariate analysis, the odds of cure were significantly lower in XDR+2sli (adjusted Odds Ratio (aOR): 0.4; 95% Confidence Interval: 0.2-0.8) compared to XDR-alone, while odds of failure+death were higher in all XDR patients with additional resistance (aOR range: 2.6-2.8).

Patients with additional resistance beyond XDR-TB showed poorer outcomes. Limitations in availability, accuracy and reproducibility of current DST methods preclude the adoption of a useful definition beyond the one currently used for XDR-TB.

Introduction

The emergence of drug resistance in the course of treatment for tuberculosis (TB) was a phenomenon recognized shortly after the introduction of streptomycin in 1946-1947 [1-2]. Acquired drug resistance in TB patients is largely an iatrogenic phenomenon [3-5], which results from the artificial selection of spontaneous drug resistance mutations in *Mycobacterium tuberculosis* during inadequate or incomplete therapy [3-5]. These drug-resistant strains can subsequently be transmitted in the community, limiting the effectiveness of combination drug-regimens used in treatment programmes.

The global epidemiology of drug resistance has worsened over the past 40 years, particularly with the emergence and increased recognition of multidrug-resistant (MDR-) TB and, more recently, extensively drug-resistant (XDR-) TB [3-5]. MDR-TB, defined as resistance to at least isoniazid and rifampicin, the two most effective first-line anti-TB drugs, requires the use of second-line anti-TB medications, which are less potent, more toxic, more expensive, and requires a longer duration of treatment [6-9]. XDR-TB is defined as MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drugs (the parenteral agents kanamycin, amikacin, or capreomycin), the two most effective classes of second-line anti-TB drugs [10]. The clinical consequences of these developments are serious. The cure rates are dramatically worse in patients infected with MDR-TB strains (40-80%) [6-9], compared with TB caused by drug-susceptible strains of *M. tuberculosis*, where it may be expected to exceed 90% in well-performing programmes [11]. When treating XDR-TB patients there are few, if any, alternative medications with which to construct a suitable treatment regimen and as a result the cure rates and survival rates are worse in patients infected with XDR-TB strains compared with MDR-TB ones [12-17].

The epidemic of highly drug-resistant TB threatens to undermine advances in TB control. The diagnosis, treatment and management of MDR-TB and XDR-TB cases require substantially greater financial and human resources, and yet yield worse outcomes [5], increasing the risk of further transmission of highly-resistant strains. The proportion of MDR-TB is very high in some areas; for example, over one-third of *newly* diagnosed TB cases in Minsk (Belarus, Eastern Europe) were MDR-TB [6]. In South Africa, although less than 5% of the reported TB cases every year were MDR-TB or XDR-TB, the management of drug-resistant TB cases absorbed more than half of the

budget of the TB programme [18].

As TB cases with resistance to an increasing number of medications are identified, there is concern that strains will emerge that are resistant to all the existing anti-TB medications. XDR-TB cases with resistance to additional second-line TB medications have already been reported [19-22]. In 2007 the acronym "XXDR-TB" (or eXtremely drug-resistant TB) was proposed to denote strains isolated from two patients which were resistant to all first- and second-line drugs *available* in a particular country [19]. The first two XXDR-TB cases, from Italy, were resistant to all first- and second-line drugs (fluoroquinolones, ethionamide, amikacin, para-aminosalycilic acid, capreomycin, kanamycin and cycloserine) and to additional drugs (rifabutin, clofazimine, dapsone, clarithromycin and thiacetazone). Subsequent reports from Iran and India [20,21] described cases resistant to all drugs tested, naming them "totally drug resistant (TDR-) TB".

Currently, there are no standardized definitions or criteria to indicate a level of TB drug resistance that is worse than XDR-TB [23]. The accuracy and reproducibility of current drug-susceptibility testing (DST) methods for agents other than those which define XDR-TB are problematic [24]. Owing to a paucity of data, it is unclear whether additional resistance beyond XDR-TB worsens prognosis , and if so, which specific drug-resistance patterns are mainly responsible.

We used individual patient data to:

1. Compare treatment outcomes between groups of TB patients with XDR with and without additional resistance to second-line injectable drugs (sli; i.e., kanamycin, amikacin and/or capreomycin), Group 4 (G4) drugs (ethionamide/prothionamide, cycloserine/terizidone and/or para-aminosalycilic acid) and other first-line drugs (ethambutol (E) and/or pyrazinamide (Z));
2. Explore the feasibility of using incremental combinations of drug resistance to develop one or more definitions of resistance beyond XDR-TB, which would have an application in both surveillance and clinical practice.

Methods

Data source

The individual patient data (''IPD'') for pulmonary MDR-TB cases which were used in this study

were contributed by investigators from 31 centres for the purposes of updating the 2011 World Health Organization's (WHO) guidelines on MDR-TB [25-27]. All studies identified in three recent systematic reviews of treatment outcomes in MDR-TB [7-9] were eligible for inclusion. Authors were contacted to share anonymized data, which included: sex, age, site of TB, chest radiography findings, sputum smear, culture and DST results (at baseline and during treatment), HIV status, anti-retroviral drug exposure, and previous treatment with first- and/or second-line anti-TB drugs. Patient-level data were also provided for anti-TB treatment regimens and associated adverse events, as well as treatment outcomes (i.e, treatment success, treatment failure, death, and default).

DST of cases included in the analysis were performed by laboratories meeting the WHO-recommended procedure for first-line drugs external quality assurance [25].

More details on the methodology of data collection and analysis are reported elsewhere[27].

Definitions

Cases which met the current XDR-TB definition and had DST performed for additional first-line and at least one Group 4 drug were included. For the purposes of the analysis, cases were split into those which had XDR without additional resistance (XDR-alone) and others which were stratified into three non-mutually exclusive groups with an incremental scale of added resistance, as follows:

- XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;
- XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;
- XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

Later-generation fluoroquinolones refers to high-dose levofloxacin, moxifloxacin and gatifloxacin. The Group 5 drugs used in patients included in this study were amoxicillin/clavulanate, clofazimine, imipenem, linezolid, thiacetazone, and clarithromycin.

Data analysis

We used simple pooling to describe clinical and treatment characteristics. Differences between sub-groups were not tested for statistical significance; since this required meta-analytic techniques and

the numbers within each sub-group, when stratified by these characteristics, were often small, the resultant estimates were frequently unstable and had large confidence intervals. The treatment outcomes among patients in different XDR-TB groups were compared to those with XDR-TB alone using two meta-analytic methods. In the first meta-analysis, we combined data from all studies using a random-effects model (PROC NLMIXED in SAS software) to calculate pooled risks and 95% confidence intervals for treatment success, treatment failure, relapse, and death during TB treatment within the aforementioned XDR-TB groups. This method uses the exact binomial likelihood approach, which accounts for study size, includes a random effect to account for inter-study heterogeneity, and produces less biased estimates of pooled effects and between-study variability [28]. In the second analysis, multivariable logistic regression random-effects meta-analysis was used to estimate the adjusted odds of treatment outcomes within the same groups of XDR-TB patients.

Duration of treatment was estimated only for those with treatment success or failure/relapse. This analysis excluded those who died or defaulted because therapy was stopped by these events. Estimates were adjusted for the following clinical covariates: age, sex, HIV infection, extent of disease (using a composite score obtained by merging sputum smear positivity and cavities on chest radiographs to define extensive disease) and previous anti-TB treatment. Proportions of treatment outcomes, stratified by XDR-TB group, were also pooled across all studies using bivariate random effect meta-analytic techniques. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, N.C.).

The study was approved by the ethics review board committees of the Montreal Chest Institute, McGill University Health Centre, and the local ethics review boards of participating centres, when necessary. It was determined to be research not involving identifiable human subjects by the U.S. Centers for Disease Control and Prevention.

Results

Out of the 9,898 cases in the original MDR-TB cohort (9,153 pulmonary cases with known treatment and treatment outcomes), 6,724 patients had DST results for at least one fluoroquinolone and one second-line injectable reported.[29] Among them 405 met the definition of XDR-TB and, thus, were included in this analysis. These were treated at 17 centres; two cohorts were initiated in

the 1980's, two between 1990 and 1995, and 13 were initiated after 1996, with patient accrual up to 2007. Most of these patients (301; 74%) had no further resistance beyond definitional XDR-alone. Among the rest, 68 (17%) met criteria for XDR+2sli, 48 (12%) for XDR+sliG4, and 42 (10%) for XDR+sliG4EZ.

Demographic and clinical profile

In all groups, the majority of patients were men, with a mean age between 40 and 46 years (Table 1). HIV co-infection was low, although slightly higher among XDR+sliG4 and XDR+sliG4EZ. The proportion of patients previously treated with second-line anti-TB drugs was low in all groups, ranging from 18 to 39%. There were no clinically important differences identified among the four groups when compared by markers of disease severity; in all four groups, over 70% of the cases had sputum smear-positive and/or cavitary disease.

Drug-susceptibility test results

Table 2a describes the DST profile of the *M. tuberculosis* isolates by each anti-TB drug tested. All XDR-TB patient groups harboured mycobacteria with a severe resistance pattern. By definition, patients in the XDR+sliG4EZ group had TB strains resistant to all first- and second-line TB medications tested; patients in the XDR+sliG4 group also demonstrated resistance to all drugs tested. Patients in the XDR-alone and XDR+2sli groups had TB strains with dramatically lower rates of resistance to the Group 4 medications, such that only 15% and 23%, respectively, were resistant to all Group 4 medications tested. XDR-alone patients also had TB strains with substantially lower rates of capreomycin (13%) and pyrazinamide (60%) resistance. Based on these differences in DST patterns, the groups varied in the median number of drugs to which the strain was resistant: 7 drugs (Inter-Quartile Range [IQR] 6-8) for XDR-alone, 9 drugs (IQR 8-10) for XDR+2sli, 8 drugs (IQR 6-10) for XDR+sliG4, and 9 drugs (IQR 6-10; Table 2b) for XDR+sliG4EZ.

Treatment for XDR-TB

The anti-TB drugs included in the treatment regimens used are shown in Table 3. Group 4 drugs were the most frequently administered, with ethionamide/prothionamide used in over 70% of patients of all the XDR-TB groups. Fewer than 20% of the patients were exposed to later generation fluoroquinolones, while ofloxacin was used in 58-77% of individuals in different XDR-TB groups. Capreomycin was most commonly used among patients in the XDR+2sli group; it was used in only

39% of the XDR-alone patients, where capreomycin resistance rates were lower. Pyrazinamide was used more frequently than ethambutol in all groups. There were minimal differences between the four XDR-TB groups in the number of drugs prescribed and in the duration of initial phase and total length of treatment (Table 4).

Treatment outcomes

Using standard meta-analysis techniques, a clear difference in the pooled proportion of patients achieving treatment success emerged when comparing XDR-alone cases (43%) to the other XDR-TB groups, with 30% cure in XDR+2sli, 34% in XDR+sliG4, and 19% in XDR+sliG4EZ. Similarly, the pooled proportion of treatment failure or death among XDR-alone patients was lower than that of the other subgroups (35% vs. ≥48%) (Table 5). Where confidence limits could be derived, these differences were shown not to be statistically significant, while exact estimates could not be calculated for the XDR+sliG4 group due to marked heterogeneity among cohorts.

In multivariable logistic regression, using XDR-alone as a reference, the adjusted odds ratio of success was statistically significantly lower in XDR+2sli (adjusted Odds Ratio [aOR]: 0.4; 95% Confidence Interval [CI]: 0.2-0.8), while odds of failure or death were consistently higher in all three XDR-TB patient groups with additional resistance (aOR range: 2.6-2.8) (Table 6a and 6b).

Differences in treatment outcomes may be explained by a significant difference in the number of possible effective drugs available for inclusion in treatment regimens. The majority of patients in the XDR+sliG4 and XDR+sliG4EZ had only 0-1 possibly effective drugs available for use, in contrast to 12% of XDR-alone patients with 0-1 possibly effective drugs (Table 7). Using current drug-resistant TB treatment guidelines, only 6% and 5% of XDR+sliG4 and XDR+sliG4EZ, respectively, and 29% of XDR+2sli, would have 4-5 possibly effective drugs with which to construct a treatment regimen. In contrast, 50% of the XDR-TB alone patients would have 4-5 potentially effective drugs available.

Discussion

This study explored treatment outcomes in patients with additional resistance beyond XDR-TB to examine the need for a new definition for more advanced drug resistance patterns. Our main finding was that patients harbouring XDR-TB strains with additional resistance had a lower likelihood of treatment success, and a higher likelihood of failure or death, than those with XDR-alone. This effect was particularly pronounced in patients resistant to both classes of second-line injectable drugs, likely underscoring the importance of these medications. Differences in risk of treatment failure and death may have also been attributable to the fact that the majority of patients had two or fewer TB drugs that were likely effective for treatment. Based on these data, patients with resistance beyond XDR-TB suffered worse outcomes, and may approximate the natural history of untreated TB disease. Efforts to prevent cases with severe drug resistance is of paramount importance.

The main strength of this study was that it allowed, for the first time, the separate analysis of outcomes of large numbers of XDR-TB patients with additional drug resistance (n=158), among a total of 405 XDR-TB cases. Moreover, individual-level data were assembled from 31 treatment centres worldwide, and underwent careful quality assurance and verification (although the XDR cases analyzed were treated in only 17 of these centres). This level of detail permitted the use of analytical techniques to adjust for differences in demographic and clinical characteristics, which are usually problematic in reviews using only aggregated data.

Using these data, we identified patients with drug resistance beyond XDR-TB. Treatment options for these patients were severely limited, with often fewer than two effective drugs remaining for treatment. Predictably, rates of treatment failure and death were significantly higher among these patients, compared to the already-poor treatment outcomes in patients with XDR-alone. Early in the TB antibiotic era, studies demonstrated the need for combination TB therapy to prevent the emergence of drug resistance and treatment failure. Patients in this study with drug resistance beyond XDR-TB may have outcomes similar to the early- or pre-antibiotic era because few treatment options are available, and the treatment options that do remain are with "Group 5" medications, whose efficacy against *M. tuberculosis* is uncertain.

The observation that XDR-2sli patients (resistant to both capreomycin and kanamycin/amikacin) fared poorly, even while susceptible to several Group 4 medications, suggests the importance of

these injectable drugs in the treatment armamentarium. Further studies examining the efficacy of second-line injectables would be helpful given that DST for these agents is considered accurate and reproducible. It would be useful to have more observations of the response to therapy in XDR-TB patients, specifically to compare outcomes in patients with strains resistant to only one second-line injectable drug vs patients whose strains are resistant to both aminoglycosides and capreomycin.

Little difference in outcomes was seen in the XDR+sliG4EZ group compared to XDR+sliG4, suggesting that resistance to ethambutol and/or pyrazinamide had little impact on prognosis. This may be because the proportion of resistance to ethambutol and pyrazinamide was high in all groups, attenuating any differences. Thus, although the use of ethambutol and pyrazinamide was associated with better treatment outcomes in some other studies [15,17], such a conclusion could not be drawn from our study.

Similarly, we examined the effect of later-generation fluoroquinolones on treatment outcomes [30]. Unfortunately, fewer than 20% of cases were prescribed later-generation fluoroquinolones, limiting our ability to test their impact. This low usage of these newer drugs may also explain the overall low proportion of patients with successful outcomes in this study. The new drugs have limited availability (related to high cost in low income settings) and our analysis also included some individuals who were treated more than 10 years ago, before these new drugs were available. It will be very helpful to compare our data with those from patient series treated more recently to quantify the added value of new fluoroquinolones in the management of XDR-TB patients [30].

Use of Group 5 drugs varied greatly and their effectiveness, safety or tolerability could not be evaluated. Until such evidence becomes available, the use by clinicians of drugs like linezolid [31] and meropenem [32] to treat TB remains “off label”. Very few XDR-TB cases were prescribed linezolid, likely due to the expense of this agent as well as the fact that most patients included in our study were treated before the introduction of linezolid. More data on the Group 5 drugs will be very welcome given that current guidance on the use of these drugs in XDR-TB is not based on sound evidence [33,34].

Details on surgical interventions were not consistently available for all patients and thus the combined impact of surgery and chemotherapy on patient outcomes could not be analysed systematically [35].

Since treatment options in patients with such advanced drug resistance are so limited, efforts must be directed at preventing such cases. Clearly, greater resources must be devoted to treatment of

drug-susceptible and MDR-TB to ensure high cure rates, and prevent the emergence of strains with second-line drug resistance. However, this study also underscores the need to prevent transmission of drug-resistant TB strains. The majority of patients in this study (61%-82%) had never been treated with second-line anti-TB medications; yet, the strains causing their disease were resistant to medications such as capreomycin, ethionamide, cycloserine and para-aminosalicylic acid, which are not routinely used for any other illness. In all likelihood, these patients had primary XDR – ie they were infected with these highly resistant TB strains. The finding that XDR-TB transmission appears to be rampant adds to existent evidence that acquisition of drug resistance by a strain is not necessarily accompanied by a "fitness defect" which compromises its transmissibility[36]. Efforts to limit transmission must be central to any strategy to combat the worldwide epidemic of drug-resistant TB.

Despite the large size of the pooled cohort and the adjustments made at analyses, it is likely that residual bias remained. Enrolment criteria could have influenced the patient mix. The predominance of a given setting, or of the prescription and management behaviours in a given setting, could have influenced the overall pooled measurements. An additional limitation was the difference in completeness of DST by the different centres (*i.e.*, which drugs were tested), the variability of intra- and inter-laboratory quality assurance and quality control for second-line anti-TB drugs. Moreover, DST for drugs other than those used to define XDR-TB present technical challenges (such as drug instability in solution, drug binding to proteins in the media, low pH requirements), require specialist input and very specific conditions. Furthermore, no standardized DST methods exist for Group 5 drugs [24,25,31,37]. Given the state of the science today, countries are therefore not advised to invest resources in developing new or additional laboratory capacity for DST to drugs for which methods are not standardised [38].

Conclusions

The current study has provided useful data to inform the future development of robust definitions for strains with more advanced drug resistance than XDR-TB. Such a definition could have application in surveillance and could be an important step towards providing better patient care, as the introduction of new drugs is now approaching [25,39-41]. The scientific discourse should continue and be complemented by well-designed studies, including those assessing the role of surgery [35] to provide high-quality data to guide future treatment recommendations.

The use of the qualifier “total drug-resistant” to describe TB strains with advanced resistance should be eschewed. First, it would be pre-mature to declare pan-resistance when there are serious limitations in the reliability of current DST methods used to test many of the TB drugs. Second, even if such technical issues were overcome, many centres would not have the resources to test reliably for all possible drugs. Third, the word “total” would be particularly inappropriate today given the imminent release of new drugs as well as others likely to be released in the foreseeable future, for which DST methods have as yet to be released. Lastly, the negative effect that a label of incurable will have on patients, contacts and care-givers is not to be discounted.

The finding that up to three-quarters of patients appeared to have primary infection with XDR-TB strains emphasizes the urgent need to tackle infection control seriously. Further studies should also examine where transmission is occurring and test strategies for halting transmission.

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Conflicts

Dennis Falzon is a staff member of the World Health Organization (WHO). The author alone is responsible for the views expressed in this publication and they do not necessarily represent the

decisions or policies of WHO.

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Table 1. Demographic and clinical profile, by XDR-TB patient group.

Variables		XDR-alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
		n = 301	*n = 68*	*n = 48*	*n = 42*
Mean age in years (standard deviation)		40.7 (13.5)	42.3 (14.4)	40.5 (15.8)	46.1 (16.6)
Males (%)		62	66	56	57
HIV infection (%†)		2	2	14	8
Sputum smear positive		78	80	78	74
Cavities on chest radiography		74	86	78	75
Extensive disease[§] (%)		78	78	74	71
Pulmonary TB only		98	95	100	100
Prior treatment (%)	None	18	24	16	18
	First-line drugs	58	37	67	62
	Second-line drugs	25	39	18	21

Percents do not always total 100% due to rounding.

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

[§] Defined as sputum smear positive on direct microscopy or in the absence of smear information, with cavities on chest radiography (see Methods)

[†] Percent of patients tested, although not all were tested

Table 2a: Drugs to which *M. tuberculosis* strains were resistant, by XDR-TB patient group.
(The number resistant / number tested are shown, with percent of resistant among those tested in parentheses. No information was collected regarding group 5 drug susceptibility test results).

	XDR alone	**XDR+2sli**	**XDR+sliG4**	**XDR+sliG4 EZ**
	n = 301 (%)	*n = 68 (%)*	*n = 48 (%)*	*n =42 (%)*
Group 1				
Ethambutol	222/280 (79)	55/68 (81)	30/30 (100)	30/30 (100)
Pyrazinamide	138/230 (60)	47/51 (92)	32/32 (100)	32/32 (100)
Group 2: Flouroquinolones*	ALL	ALL	ALL	ALL
Group 3				
Streptomycin	208/292 (71)	68/68 (100)	27/27† (100)	26/26† (100)
Kanamycin/Amikacin**	279/301 (93)	68/68 (100)	48/48 (100)	42/42 (100)
Capreomycin	26/207 (13)	68/68 (100)	48/48† (100)	12/12† (100)
Resistant to Kanamycin/Amikacin and Capreomycin	14/301 (5)	68/68 (100)	12/12† (100)	12/12† (100)
Resistant to all injectables ***	0/301 (0)	68/68 (100)	12/12† (100)	12/12† (100)
Group 4 ****				
Ethionamide or prothionamide	138/257 (54)	38/64 (59)	47/47 (100)	41/41 (100)
Cycloserine or terizidone	59/235 (25)	12/59 (20)	26/26 (100)	26/26 (100)
Para-aminosalycilic acid	87/228 (38)	26/56 (46)	21/21 (100)	21/21 (100)
Resistant to less than half of Group 4 drugs tested	164 (63)	40 (61)	0	0
Resistant to half or two thirds of Group 4 drugs tested	60 (23)	11 (17)	0	0
Resistant to all Group 4 tested	38 (15)	15 (23)	48 (100)	42 (100)

* All patients were by definition resistant to fluoroquinolones as they all met the definition of extensive drug resistance. Nearly all laboratories reported a single result for fluoroquinolones susceptibility testing – generally for ofloxacin susceptibility.

** Kanamycin and amikacin susceptibility results are shown together because participating laboratories tested for 1 drug or the other but very few tested for both. Hence these results were considered equivalent as 1 result.

*** Resistant to streptomycin, kanamycin, amikacin and capreomycin.

**** Group 4 drugs resistance was categorized them into: resistant to less than half of tested, resistant to half or two-thirds of tested, and resistant to all group 4 drugs tested.

† In these groups, patients were resistant to all injectables tested, but the minimum requirement was that they were tested for susceptibility to kanamycin/amikacin. Hence many were not tested for susceptibility to capreomycin and/or streptomycin.

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

Table 2b. Total number of TB drugs to which *M. tuberculosis* strains were resistant, by XDR-TB patient group.

Number of drugs to which the strain was resistant*	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
	n = 301	*n = 68*	*n = 48*	*n =42*
5	9	0	10	0
6	31	4	27	29
7	31	13	8	10
8	18	31	6	7
9	10	25	4	5
10	1	21	35	40
11	0	6	8	10

Values correspond to the percentage of patients. Column totals may exceed 100% due to rounding.

* The number of drugs includes isoniazid, rifampicin, and at least one fluoroquinolone, and one second-line injectable, so all patients were resistant to at least one additional drug of these four drugs.

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

Table 3. Percentage of patients receiving specific anti-tuberculosis drugs during treatment episode analyzed, by XDR-TB patient group.

Drugs administered	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
	n = 301	*n = 68*	*n = 48*	*n = 42*
Group 1				
Pyrazinamide	54	49	73	69
Ethambutol	43	37	50	48
Group 2				
Ofloxacin	58	69	77	74
Later generation fluoroquinolones	17	16	6	7
Group 3				
Kanamycin	37	12	54	48
Amikacin	13	6	2	2
Capreomycin	39	69	15	17
Streptomycin	20	6	8	10
Group 4				
Group 4, any drug	96	94	83	81
Ethionamide or Prothionamide	79	76	75	74
Cycloserine or Terizidone	88	88	48	48
Para-aminosalycilic acid	65	57	29	31
Group 5: any drug	45	51	17	19

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

Table 4. Number of anti-tuberculosis drugs prescribed and duration of therapy, by XDR-TB patient group.

	XDR alone	**XDR+2sli**	**XDR+sliG4**	**XDR+sliG4EZ**
	n = 301	*n = 68*	*n = 48*	*n = 42*
Number of prescribed drugs				
Initial phase	5.2 (1.1)	5.3 (1.1)	5.0 (0.8)	4.9 (0.9)
Continuation phase	4.1 (1.0)	4.5 (0.7)	3.7 (0.8)	3.7 (0.8)
Duration of therapy*				
Initial phase, months	9.8 (6.5)	12.0 (7.5)	6.3 (8.2)	6.8 (8.7)
Total therapy, months	22.4 (17.8)	18.1 (12.3)	16.5 (5.7)	16.5 (6.2)

Data correspond to mean (standard deviation).

*Duration of treatment estimated only for those with treatment success or failure/ relapse. This analysis excludes those who died or defaulted, as therapy was truncated by these events.

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

Table 5. Pooled treatment outcomes, by XDR-TB patient group.

Treatment outcome	XDR alone	XDR+2sli	XDR+sliG4†	XDR+sliG4EZ
Treatment success	43 (27, 58)	30 (17, 43)	34 (-, -)	19 (0, 48)*
Treatment failure	20 (15, 25)	29 (8, 50)	33 (-, -)	26 (14, 38)
Died	13 (6, 20)	18 (7, 29)	30 (18, 41)*	35 (21, 50)*
Treatment failure or died	35 (26, 45)	54 (40, 69)*	48 (-, -)	49 (37, 61)
Defaulted	15 (5, 24)	15 (3, 27)	18 (-, -)	19 (6, 32)

Values correspond to the percentage of patients in each treatment category as derived by random effects bivariate estimates, followed by the 95% confidence limits in parentheses (see Methods).

†Pooled estimates unstable and 95% confidence intervals could not be calculated for some outcomes.

* Numbers do not always total to 100% - due to rounding, and meta-analytic pooling methods

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

Table 6. Odds of treatment outcomes, by XDR-TB patient group.

A. *Univariable random effects logistic regression (pooled unadjusted odds)*

Treatment outcome	XDR-alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
	n = 301	*n = 68*	*n = 48*	*n =42*
Treatment success	1.0 (reference)	**0.4 (0.2, 0.8)**	0.6 (0.2, 1.6)	0.6 (0.2. 1.8)
Treatment failure	1.0 (reference)	1.8 (0.7, 4.5)	1.5 (0.6, 3.7)	1.5 (0.6, 3.9)
Died	1.0 (reference)	1.8 (0.7, 4.7)	1.6 (0.6, 4.5)	1.7 (0.6, 4.8)
Treatment failure or died	1.0 (reference)	**2.4 (1.2, 4.8)**	**2.2 (1.0, 5.1)**	**2.4 (1.0, 5.9)**
Defaulted	1.0 (reference)	1.0 (0.4, 2.6)	0.6 (0.2, 1.7)	0.5 (0.2, 1.8)

B. Multivariable random effects logistic regression (pooled adjusted odds)*

Treatment outcome	XDR-alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
	n = 301	*n = 68*	*n = 48*	*n =42*
Treatment success	1.0 (reference)	**0.4 (0.2, 0.8)**	0.6 (0.2, 1.6)	0.5 (0.2, 1.7)
Treatment failure	1.0 (reference)	**2.1 (1.0, 4.5)**	1.8 (0.7, 4.7)	1.9 (0.7, 5.3)
Died	1.0 (reference)	1.6 (0.6, 4.4)	1.7 (0.6, 4.9)	1.8 (0.6, 5.3)
Treatment failure or died	1.0 (reference)	**2.6 (1.2, 4.4)**	**2.6 (1.1, 6.7)**	**2.8 (1.0, 7.9)**
Defaulted	1.0 (reference)	1.0 (0.3, 2.6)	0.5 (0.2, 1.8)	0.5 (0.1, 2.0)

*Adjusted for age, sex, HIV co-infection, severity of disease, and previous treatment episodes with first- or second-line TB drugs.

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.

Table 7: Number of possibly effective drugs included in treatment regimens, by XDR-TB patient group.

Number of possibly effective drugs in regimen	**XDR-alone** *n* = **301**		**XDR+2sli** *n* = **68**		**XDR+sliG4** *n* = **48**		**XDR+sliG4EZ** *n* = **42**	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
0 – 1	36	12	10	15	36	75	35	83
2	41	14	23	34	5	10	2	5
3	76	25	15	22	4	8	3	7
4	68	23	9	13	1	2	0	0
5	80	27	11	16	2	4	2	5

* Possibly effective means sensitive, or not tested for that drug. All group 5 drugs considered possibly effective because no DST available for these drugs. Later generation fluoroquinolones considered possibly effective, even though (by definition) all patients' isolates were resistant to fluoroquinolones.

-XDR+2sli: XDR-TB, plus resistance to both an aminoglycoside injectable (kanamycin/amikacin) and to capreomycin;

-XDR+sliG4: XDR-TB, plus resistance to all second-line TB drugs tested, with as a minimum, resistance to kanamycin and to at least one Group 4 drug;

-XDR+sliG4EZ: XDR-TB, plus resistance to all first- and second-line TB drugs tested, with as a minimum resistance to kanamycin, one Group 4 drug and either pyrazinamide and/or ethambutol.