Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis

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ABSTRACT The broadest pattern of tuberculosis (TB) drug resistance for which a consensus definition exists is extensively drug-resistant (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 in order 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 nonmutually exclusive XDR-TB patient groups: XDR plus resistance to all the second-line injectables (sli) and capreomycin and kanamycin/amikacin (XDR+2sli) XDR plus resistance to second-line injectables and to more than one group 4 drug, *i.e.* ethionamide/protionamide, cycloserine/terizidone or para-aminosalicylic acid (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 OR 0.4, 95% CI 0.2–0.8) compared to XDR alone, while odds of failure and death were higher in all XDR patients with additional resistance (adjusted OR 2.6–2.8).

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

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Drug resistance beyond extensively drug-resistant tuberculosis: patients with additional resistance have poorer outcomes http://ow.ly/kFUA3

Received: Aug 29 2012 | Accepted after revision: Sept 20 2012 | First published online: Oct 11 2012

Introduction

The emergence of drug resistance in the course of treatment for tuberculosis (TB) is a phenomenon that was recognised shortly after the introduction of streptomycin in 1946–1947 [1, 2]. Acquired drug resistance in TB patients is largely an iatrogenic phenomenon, 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 require 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 cure rates of >90% may be expected in successful 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 strains [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, 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) were MDR-TB [6]. In South Africa, although <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 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 [20] and India [21] described cases resistant to all drugs tested, naming them ''totally drug resistant-TB''.

Currently, there are no standardised 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-TB with and without additional resistance to second-line injectable drugs (sli; *i.e.* kanamycin, amikacin and/or capreomycin), group 4 (G4) drugs (ethionamide/protionamide, cycloserine/terizidone

For editorial comments see page 5.

Support statement: Funding for this study was provided, in part, by the Stop TB Department of the World Health Organization, through a grant from USAID. Funding for data gathering at participating centres was provided in: the State of California from the Centers for Disease Control Cooperative Agreement Funds; Mexico (Veracruz) from the Mexican Secretariat of Health, the National Institutes of Health of the United States (A135969 and K01TW000001), the Wellcome Trust (176W009), the Howard Hughes Medical Institute (55000632), and the Mexican Council of Science and Technology (SEP 2004-C01-47499, FOSSIS 2005–2 (14475), (87332)) South Africa from the South African Medical Research Council funding. M. Bauer and D. Menzies were supported by salary awards from the Fonds de Recherche en Santé de Québec; G.B. Migliori and R. Centis receive support from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement FP7-223681; L. Shah was supported by the Canadian Institutes of Health Research (Canada Graduate Scholarship) and N. Gandhi received a Doris Duke Charitable Foundation Clinical Scientist Development Award.

Conflict of interest: None declared.

DOI: 10.1183/09031936.00136312

and/or para-aminosalycilic acid) and other first-line drugs (ethambutol (E) and/or pyrazinamide (Z)) and 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 both in surveillance and in clinical practice.

Methods

Data source

The individual patient data for pulmonary MDR-TB cases 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 anonymised data, which included sex, age, site of TB, chest radiography findings, sputum smear, culture and DST results (at baseline and during treatment), HIV status, antiretroviral 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 was performed by laboratories meeting the WHO-recommended procedure for external quality assurance of first-line drugs [25]. More details on the methodology of data collection and analysis have been reported elsewhere [27].

Definitions

Cases which met the current XDR-TB definition and had DST performed for additional first-line drugs 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 nonmutually 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 subgroups were not tested for statistical significance; since this required meta-analytic techniques and the numbers within each subgroup, 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; SAS Institute, Cary, NC, USA) 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 interstudy 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).

The study was approved by the ethics review board committees of the Montreal Chest Institute, McGill University Health Centre (Montreal, Canada), and the local ethics review boards of participating centres,

when necessary. It was determined to be research not involving identifiable human subjects by the US Centers for Disease Control and Prevention.

Results

Out of the 9898 cases in the original MDR-TB cohort (9153 pulmonary cases with known treatment and treatment outcomes), 6724 patients had reported DST results for at least one fluoroquinolone and one second-line injectable [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 1980s, two between 1990 and 1995 and 13 were initiated after 1996, with patient accrual up to 2007. Most of these patients (n=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 male, with a mean age of 40–46 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 >70% of the cases had sputum smear-positive and/or cavitary disease.

Drug susceptibility test results

Table 2 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: seven drugs (interquartile range (IQR) 6–8) for XDR alone; nine drugs (IQR 8–10) for XDR+2sli; eight drugs (IQR 6–10) for XDR+sliG4; and nine drugs (IQR 6–10) for XDR+sliG4EZ (table 3).

Treatment for XDR-TB

The anti-TB drugs included in the treatment regimens used are shown in table 4. Group 4 drugs were the most frequently administered, with ethionamide/prothionamide used in >70% of patients of all the XDR-TB groups. <20% of the patients were exposed to later generation fluoroquinolones, while ofloxacin was

TABLE 1 Demographic and clinical profile by the extensively drug-resistant tuberculosis (XDR-TB) patient group

	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
Subjects n	301	68	48	42
Age years	40.7±13.5	42.3±14.4	40.5±15.8	46.1±16.6
Male	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

Data are presented as mean±SD or %, unless otherwise stated. Percentages do not always total 100% due to rounding. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 tuberculosis drugs tested, with, as a minimum, resistance to kanamycin and to at least one group 4 drug (G4); 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 (Z) and/or ethambutol (E). [#]: percentage of patients who were tested; not all were tested; [¶]: defined as sputum smear-positive on direct microscopy or in the absence of smear information, with cavities on chest radiography (see Methods section).

DOI: 10.1183/09031936.00136312

TABLE 2 Drugs to which *Mycobacterium tuberculosis* strains were resistant by extensively drug-resistant tuberculosis (XDR-TB) patient group

	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
Subjects	301	68	48	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				
Fluoroquinolones[#]	301/301 (100)	68/68 (100)	48/48 (100)	42/42 (100)
Group 3				
Streptomycin	208/292 (71)	68/68 (100)	27/27[f] (100)	26/26[f] (100)
Kanamycin/amikacin[¶]	279/301 (93)	68/68 (100)	48/48 (100)	42/42 (100)
Capreomycin	26/207 (13)	68/68 (100)	48/48[f] (100)	12/12[f] (100)
Resistant to kanamycin/amikacin and capreomycin	14/301 (5)	68/68 (100)	12/12[f] (100)	12/12[f] (100)
Resistant to all injectables[+]	0/301 (0)	68/68 (100)	12/12[f] (100)	12/12[f] (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 drugs tested	38 (15)	15 (23)	48 (100)	42 (100)

Data are presented as n, n/N (%) or n (%). No information was collected regarding group 5 drug susceptibility test results. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 (G4); 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 (Z) and/or ethambutol (E). [#]: 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 one drug or the other but very few tested for both. Hence these results were considered equivalent. [+]: resistant to streptomycin, kanamycin, amikacin and capreomycin. [§]: group 4 drug resistance was categorised as: resistant to less than half of those tested; resistant to half or two-thirds of those tested; and resistant to all group 4 drugs tested. [f]: 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.

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 5).

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% *versus* $\geqslant$48%) (table 6). 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 OR 0.4, 95% CI 0.2–0.8), while odds of failure or death were consistently higher in all three XDR-TB patient groups with additional resistance (adjusted OR range 2.6–2.8) (table 7).

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 one or no possibly effective drug available for use, in contrast to 12% of XDR alone patients with one or no possibly effective drugs (table 8). Using current drug-resistant TB treatment guidelines, only 6% and 5% of XDR+sliG4 and XDR+sliG4EZ, respectively, and 29% of XDR+2sli, would

TABLE 3 Total number of tuberculosis (TB) drugs to which *Mycobacterium tuberculosis* strains were resistant by extensively drug-resistant (XDR)-TB patient group

	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
Subjects n	301	68	48	42
Number of drugs to which the strain was resistant#				
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

Data are presented as %, unless otherwise stated. Column totals may exceed 100% due to rounding. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 (G4) 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 (Z) and/or ethambutol (E). #: 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 drug in addition to these four.

have four or five possibly effective drugs with which to construct a treatment regimen. In contrast, 50% of the XDR-TB alone patients would have four or five 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, underscoring the likely

TABLE 4 Patients receiving specific anti-tuberculosis (TB) drugs analysed by extensively drug-resistant (XDR)-TB patient group

	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
Subjects n	301	68	48	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 protionamide	79	76	75	74
Cycloserine or terizidone	88	88	48	48
Para-aminosalycilic acid	65	57	29	31
Group 5	45	51	17	19

Data are presented as %, unless otherwise stated. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 (G4) 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 (Z) and/or ethambutol (E).

DOI: 10.1183/09031936.00136312

TABLE 5 Number of anti-tuberculosis (TB) drugs prescribed and duration of therapy by extensively drug-resistant (XDR)-TB patient group

	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
Subjects	301	68	48	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[#] months				
Initial phase	9.8±6.5	12.0±7.5	6.3±8.2	6.8±8.7
Total therapy	22.4±17.8	18.1±12.3	16.5±5.7	16.5±6.2

Data are presented as n or mean±SD. This analysis excludes those who died or defaulted, as therapy was truncated by these events. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 (G4); 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 (Z) and/or ethambutol (E). [#]: duration of treatment estimated only for those with treatment success or failure/relapse.

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 to be 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 are 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 analysed 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.

TABLE 6 Pooled treatment outcomes by extensively drug-resistant tuberculosis (XDR-TB) patient group

	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)
Death	13 (6–20)	18 (7–29)	30 (18–41)[¶]	35 (21–50) [¶]
Treatment failure or death	35 (26–45)	54 (40–69)[¶]	48	49 (37–61)
Defaulted	15 (5–24)	15 (3–27)	18	19 (6–32)

Data are presented as % (95% CI) or %. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 (G4) 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 (Z) and/or ethambutol (E). [#]: pooled estimates were unstable and 95% confidence intervals could not be calculated for some outcomes; [¶]: numbers do not always total 100% due to rounding and meta-analytic pooling methods.

TABLE 7 Odds of treatment outcomes by extensively drug-resistant tuberculosis (XDR-TB) patient group

	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
Subjects	301	68	48	42
Univariable random effects logistic regression (pooled unadjusted odds)				
Treatment success	1.0 (ref.)	**0.4 (0.2–0.8)**	0.6 (0.2–1.6)	0.6 (0.2–1.8)
Treatment failure	1.0 (ref.)	1.8 (0.7–4.5)	1.5 (0.6–3.7)	1.5 (0.6–3.9)
Death	1.0 (ref.)	1.8 (0.7–4.7)	1.6 (0.6–4.5)	1.7 (0.6–4.8)
Treatment failure or death	1.0 (ref.)	**2.4 (1.2–4.8)**	**2.2 (1.0–5.1)**	**2.4 (1.0–5.9)**
Defaulted	1.0 (ref.)	1.0 (0.4–2.6)	0.6 (0.2–1.7)	0.5 (0.2–1.8)
Multivariable random effects logistic regression (pooled adjusted odds[#])				
Treatment success	1.0 (ref.)	**0.4 (0.2–0.8)**	0.6 (0.2–1.6)	0.5 (0.2–1.7)
Treatment failure	1.0 (ref.)	**2.1 (1.0–4.5)**	1.8 (0.7–4.7)	1.9 (0.7–5.3)
Death	1.0 (ref.)	1.6 (0.6–4.4)	1.7 (0.6–4.9)	1.8 (0.6–5.3)
Treatment failure or death	1.0 (ref.)	**2.6 (1.2–4.4)**	**2.6 (1.1–6.7)**	**2.8 (1.0–7.9)**
Defaulted	1.0 (ref.)	1.0 (0.3–2.6)	0.5 (0.2–1.8)	0.5 (0.1–2.0)

Data are presented as n or OR (95% CI). Statistically significant results are presented in bold type. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 (G4); 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 (Z) and/or ethambutol (E); ref.: reference. [#]: adjusted for age, sex, HIV co-infection, severity of disease and previous treatment episodes with first- or second-line TB drugs.

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 *versus* patients whose strains are resistant to both aminoglycosides and capreomycin.

Little difference in outcomes was seen in the XDR+sliG4EZ group compared with the XDR+sliG4 group, 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

TABLE 8 Number of possibly effective drugs included in treatment regimens by extensively drug-resistant tuberculosis (XDR-TB) patient group

	XDR alone	XDR+2sli	XDR+sliG4	XDR+sliG4EZ
Subjects	301	68	48	42
Number of possibly effective drugs				
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)

Data are presented as n or n (%). Possibly effective means sensitive, or not tested for that drug. All group 5 drugs were considered possibly effective because no drug susceptibility testing was available for these drugs. Later generation fluoroquinolones were considered possibly effective, even though (by definition) all patients' isolates were resistant to fluoroquinolones. XDR alone: resistance to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drug (sli); 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 (G4) 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 (Z) and/or ethambutol (E).

DOI: 10.1183/09031936.00136312

any differences. Thus, although the use of ethambutol and pyrazinamide has been 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, <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 >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, probably 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 to 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-TB, *i.e.* they were infected with these highly resistant TB strains. The finding that XDR-TB transmission appears to be rampant adds to existing evidence that the 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 interlaboratory quality assurance and quality control for second-line anti-TB drugs. Moreover, DST for drugs other than those used to define XDR-TB presents technical challenges (such as drug instability in solution, drug binding to proteins in the media and low pH requirements), requires specialist input and very specific conditions. Furthermore, no standardised 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 ''totally drug resistant'' to describe TB strains with advanced resistance should be eschewed. First, it would be premature to declare pan-resistance when there are serious limitations in the reliability of current DST methods used to test many of the TB drugs available. Secondly, even if such technical issues were overcome, many centres would not have the resources to test reliably for all possible drugs. Thirdly, 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 caregivers is not to be discounted.

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

Acknowledgements

The Members of The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB are as follows. S. Ahuja (Long Island City, NY, USA), D. Ashkin (Lantana, FL, USA), M. Avendano (Toronto, ON, Canada), R. Banerjee (Rochester, MN, USA), J.N. Bayona (Hanover, NH, USA), M.C. Becerra (Boston, MA, USA), A. Benedetti (Montreal, QC, Canada), M. Burgos (Albuquerque, NM, USA), C-Y. Chiang (Taipei, Taiwan), H. Cox (Cape Town, South Africa), N.H. Dung (Ho Chi Minh City, Vietnam), D. Enarson (Paris, France), K. Flanagan (Fajara, The Gambia), J. Flood (Richmond, CA, USA), L. Garcia-Garcia (Cuernavaca, Mexico), R.M. Granich (Geneva, Switzerland), M.D. Iseman (Denver, CO, USA), L.G. Jarlsberg (San Francisco, CA, USA), H.R. Kim (Seoul, South Korea), W.J. Koh (Seoul, South Korea), J. Lancaster (Pretoria, South Africa), C. Lange (Borstel, Germany), W.C.M. de Lange (Haren, the Netherlands), V. Leimane (Upeslejas, Latvia), C.C. Leung (Hong Kong, China), J. Li (New York, NY, USA), S.P. Mishustin (Tomsk, Russian Federation), C.D. Mitnick (Boston, MA, USA), M. Narita (Seattle, WA, USA), P. O'Riordan (London, UK), M. Pai (Montreal, QC, Canada), S.K. Park (Masan City, South Korea), G. Pasvol (London, UK), J. Pena (Madrid, Spain), A. Ponce-de-Leon (Mexico City, Mexico), M.I.D. Quelapio (Makati, Philippines), V. Riekstina (Upeslejas, Latvia), J. Robert (Paris, France), S. Royce (San Francisco, CA, USA), K.J. Seung (Boston, MA, USA), L. Shah (Montreal, QC, Canada), T.S. Shim (Seoul, South Korea), S.S. Shin (Boston, MA, USA), Y. Shiraishi (Tokyo, Japan), J. Sifuentes-Osornio (Mexico City, Mexico), M.J. Strand (Denver, CO, USA), P. Tabarsi (Tehran, Iran), T.E. Tupasi (Makati, Philippines), R. van Altena (Groningen, the Netherlands), M. Van der Walt (Pretoria, South Africa), T.S. Van der Werf (Groningen, the Netherlands), P. Viiklepp (Tallinn, Estonia), J Westenhouse (Richmond, CA, USA), W.W. Yew (Hong Kong, China), and J.J. Yim (Seoul, South Korea).

D. 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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