Changes in treatment for multidrug-resistant tuberculosis according to national income

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Introduction of group A drugs is probably responsible for improved outcomes, even in resource-poor countries. However, a gap in treatment outcomes, which could not be fully explained by group A drugs, persists between high- and upper-middle-income countries https://bit.ly/2XJpO8U

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ABSTRACT The aim of this study was to analyse temporal changes in treatments for and outcomes of multidrug-resistant (MDR)/rifampin-resistant (RR)-tuberculosis (TB) in the context of national economic status.

We analysed data collected by the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB Treatment on MDR/RR-TB patients from 37 countries. The data were stratified by three national income levels (low-/lower-middle, upper-middle and high) and grouped by time of treatment initiation (2001–2003, 2004–2006, 2007–2009, 2010–2012 and 2013–2015). Temporal trends over the study period were analysed. The probability of treatment success in different income groups over time was calculated using generalised linear mixed models with random effects.

In total, 9036 patients were included in the analysis. Over the study period, use of group A drugs (levofloxacin/moxifloxacin, bedaquiline and linezolid) recommended by the World Health Organization increased and treatment outcomes improved in all income groups. Between 2001–2003 and 2013–2015, treatment success rates increased from 60% to 78% in low-/lower-middle-income countries, from 40% to 67% in upper-middle-income countries, and from 73% to 81% in high-income countries. In earlier years, the probability of treatment success in upper-middle-income countries was lower than that in low-/lower-middle-income countries, but no difference was observed after 2010. However, high-income countries had persistently higher probability of treatment success compared to upper-middle income countries.

Improved treatment outcomes and greater uptake of group A drugs were observed over time for patients with MDR/RR-TB at all income levels. However, treatment outcomes are still unsatisfactory, especially in upper-middle-income countries.

Introduction

Drug-resistant tuberculosis (TB) is a major threat to global health. In 2018, approximately half a million cases of rifampin-resistant (RR)-TB occurred globally [1]. Among patients with RR-TB, 78% had multidrug-resistant (MDR)-TB, defined as resistance to both isoniazid and rifampin [1]. The number of reported cases of MDR/RR-TB is increasing, with ∼214 000 MDR/RR-TB-associated deaths occurring in 2018 [1].

Globally, the treatment success rate for MDR/RR-TB has been a disappointing 56% [1]. Antimicrobial therapy for MDR/RR-TB requires long durations of treatment. Under some circumstances, parenteral administration of drugs such as amikacin or streptomycin for 6–7 months may be required [2]. Treatment-associated adverse events are reported frequently [3–5].

Over the past two decades, several improvements have been made in the treatment of patients affected by MDR/RR-TB [6]. Later-generation fluoroquinolones, such as levofloxacin and moxifloxacin, have replaced the earlier-generation fluoroquinolones. Novel anti-TB drugs (*e.g.* bedaquiline and delamanid) have been introduced [7–9] and existing drugs (*e.g.* linezolid, carbapenem and clofazimine) have been repurposed to treat patients with MDR/RR-TB [10–12]. These drugs enabled the adoption of all-oral regimens in the current guideline [2]. Finally, universal adoption of the Xpert MTB/RIF assay has shortened the turnaround time for MDR/RR-TB diagnosis, enabling earlier treatment initiation [13].

Together, 20 countries, including upper-middle-income, lower-middle-income and low-income countries, account for 86% of global MDR/RR-TB incidence [1]. In some of these countries, the availability of later-generation fluoroquinolones, second-line injectable drugs and linezolid have been sparse [14–16]. Since the early 2000s, the Global Fund to Fight AIDS, Tuberculosis and Malaria has reduced the prices of second-line drugs in resource-poor settings [17]. In addition, bedaquiline is distributed at reduced prices or free of charge in low-income countries [18].

With the introduction of new drugs and improved treatment strategies for MDR-TB, treatment outcomes might improve. However, there have been few reports of changes in treatment modalities and outcomes among MDR/RR-TB patients over time, and there have been no analyses of these factors in the context of national income levels. This study aimed to analyse temporal changes in patient characteristics, drug susceptibility patterns, treatment modalities and treatment outcomes in the context of national economic status using a large MDR/RR-TB patient dataset.

Material and methods

Data collection

We analysed data collected by the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB Treatment, which included datasets from 50 studies conducted in over 37 countries (supplementary table S1) [11]. The analysis was restricted to patients enrolled in observational studies who commenced treatment between January 1, 2001 and December 31, 2015. To reflect real-world practice, patients enrolled in randomised controlled trials were excluded. Additionally, to prevent distortion of results by a single study with many participants, we randomly selected a 10% sample from the 3626 patients included in a South African cohort study conducted in 2015.

Patients were classified into three groups based on World Bank categories of per capita gross national income in 2015 (in USD) [19] as follows: low/lower-middle-income (⩽4035), upper-middle-income (4036–12 475) and high-income (⩾12 476). In addition, the patients were grouped by 3-year intervals according to the year that treatment commenced: 2001–2003, 2004–2006, 2007–2009, 2010–2012 and 2013–2015.

Treatment outcomes were defined based on the recommendations of the World Health Organization (WHO) [20] and Laserson *et al.* [21] (supplementary table S1). Outcomes were classified as "success", "treatment failure or relapse", "death" and "loss to follow-up or transfer". In our analysis, treatment success was defined as the sum of cures and treatment completions without evidence of relapse. Follow-up data after treatment completion were not available to define "cure" [22].

Data analysis

Baseline demographic characteristics (age, sex, body mass index, smoking status, HIV infection and diabetes mellitus), previous TB treatment history with first-line or second-line anti-TB drugs, acid-fast

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bacilli (AFB) smear status, radiographic features (presence of cavity or bilateral involvement), drug susceptibility patterns, treatment modalities (including drug use, hospitalisation and surgical resection) and treatment outcomes were compared across World Bank categories of per capita gross national income and 3-year intervals of treatment initiation.

Dichotomous variables were presented as frequencies (%) and continuous variables were described using medians and interquartile ranges (IQRs). Descriptive analyses were performed using complete case data without missing data imputation. Comparisons of continuous and dichotomous variables by income groups were made using the Kruskal–Wallis and Chi-squared tests, respectively. Tests for trend were used to analyse temporal changes over the study period.

Regression analyses used data where missing values were multiply imputed. Data on patient characteristics and drug susceptibility testing (DST) were imputed separately. Patient characteristics were imputed using demographic factors, previous treatment history, radiographic features, treatment outcomes and income level. Data on DST were imputed based on demographic factors, previous treatment history, DST, radiographic features, treatment outcomes and income level.

The primary analysis was treatment success *versus* all other outcomes (treatment failure or relapse, death and loss to follow-up or transfer), using imputed data. We also assessed survival (death *versus* all other outcomes). The odds ratio was calculated with 95% confidence intervals to identify treatment-related factors affecting treatment outcomes among different income groups over time, using generalised linear mixed-models with each study acting as the clustering variable. The resulting models included the unadjusted model (model 1) and stepwise models adjusted for 1) demographic characteristics (model 2); 2) all variables included in model 2 plus radiographic features, AFB smear status and previous TB treatment history (model 3); 3) all variables included in model 3 plus DST (model 4); and 4) all variables included in model 4 plus group A drugs (levofloxacin/moxifloxacin, bedaquiline and linezolid) according to a recent WHO classification [2] (model 5).

Data were collated and analysed using R (version 3.5.1) and the R lme4 package (version 1.1.21). Multiple imputations were performed using the R Multiple Imputation with Chained Equations (MICE) package (version 3.6.0). Values of $p<0.05$ were considered statistically significant. The study was approved by the institutional review board of McGill University Health Centre (Montreal, QC, Canada) and ethics approval was obtained from each participating institution.

Results

Patient classification, demographics and clinical characteristics

9036 patients with MDR/RR-TB started treatment between January 1, 2001 and December 31, 2015 and were included in the analysis. The dataset included 2612 (29%) patients from low-/lower-middle-income countries, 3926 (43%) from upper-middle-income countries and 2498 (28%) from high-income countries (table 1). The list of countries included in the analysis along with the number of patients from each country is shown in supplementary table S2.

The prevalence of HIV infection (39%) was highest in patients from upper-middle-income countries (table 1), and yet the use of antiretroviral therapy was lowest in the upper-middle income group (47%) as compared to the low-/low-middle (90%) and high (78%) income groups (supplementary table S3). Full data on patient demographics including smoking history and diabetes are provided in supplementary table S3. History of treatment with second-line anti-TB drugs was more common in upper-middle-income (31%) countries than in low-/lower-middle-income (13%) and high-income (22%) countries. History of treatment with second-line anti-TB drugs increased among all patients (pooled irrespective of income) over time, peaking in the 2007–2009 period at 26% and maintaining at this level for the remaining two time periods (table 2). Presence of cavities on chest radiographs was also more common in upper-middle-income countries (68%) than in low-/lower-middle-income (55%) and high-income (58%) countries (supplementary table S4).

Resistance to fluoroquinolones was more common in upper-middle-income countries (27%) than in low-/lower-middle-income (21%) and high-income (23%) countries (table 3). Resistance to any second-line injectable drug was also more common among patients from upper-middle-income countries (33%) than among those from low-/lower-middle-income (17%) and high-income (28%) countries (table 3). Among all patients (pooled irrespective of income), resistance to fluoroquinolones and second-line injectable drugs increased over time (table 3). Drug susceptibility patterns for other drugs are shown in supplementary table S5.

Treatment modalities

Overall, use of later-generation fluoroquinolones was more common among patients in high-income (77%) and low-/lower-middle-income (74%) countries than among those in upper-middle-income (32%)

TABLE 1 Baseline characteristics of 9036 patients with multidrug-resistant/rifampin-resistant tuberculosis

	Period 1 2001–2003	Period 2 2004–2006	Period 3 2007–2009	Period 4 2010–2012	Period 5 2013–2015	p-value trend over time	Total 2001–2015
Subjects	1374	1948	2737	1750	1230		9036
Age years							
Total	34 (27–43)	36 (28–47)	36 (28–46)	36 (27–46)	35 (27–46)	0.15	36 (28–46)
Low-/lower-middle	37 (30–48)	37 (29–47)	37 (27–47)	35 (26–44)	29 (22–38)	<0.001	36 (27–46)
Upper-middle	33 (26–41)	35 (28–44)	36 (29–45)	32 (25–43)	35 (27–45)	0.001	34 (27–44)
High	39 (29–51)	38 (28–50)	37 (28–48)	38 (30–50)	39 (30–52)	0.1	38 (29–50)
Male							
Total	845 (61)	1227 (63)	1687 (62)	1090 (62)	743 (60)	0.485	5592 (62)
Low-/lower-middle	118 (66)	383 (62)	587 (68)	492 (59)	70 (53)	0.012	1650 (63)
Upper-middle	640 (61)	349 (63)	661 (56)	206 (64)	476 (58)	0.26	2332 (59)
High	87 (63)	495 (64)	439 (62)	392 (66)	197 (71)	0.052	1610 (64)
BMI kg·m^{-2}							
Total	18.7 (15.7–21.7)	19.6 (17.2–21.7)	20 (17.7–22.6)	19.7 (17.9–21.8)	20.1 (18.3–22.4)	<0.001	19.7 (17.6–22.1)
Low-/lower-middle	18.6 (15.7–21.9)	18.8 (16.4–21.5)	19.9 (17.4–22.7)	19.1 (17.6–20.8)	17.6 (15.2–21.2)	0.03	19.3 (17–21.7)
Upper-middle	19.1 (15.7–21.1)	19.7 (17.4–21.7)	19.9 (17.6–22.3)	20 (18.2–22.4)	20.3 (18.2–23.1)	<0.001	19.8 (17.6–22.3)
High	NA	19.7 (18.8–22.1)	20.4 (18.7–22.7)	20.3 (18.5–22.4)	20 (18.6–21.8)	0.63	20.2 (18.7–22.3)
HIV infection							
Total	321 (36)	242 (13)	511 (19)	133 (8)	418 (34)	0.001	1625 (20)
Low-/lower-middle	0 (0)	1 (0)	33 (4)	73 (9)	39 (30)	<0.001	146 (6)
Upper-middle	310 (53)	190 (37)	452 (39)	13 (4)	349 (43)	0.003	1314 (39)
High	11 (9)	51 (7)	26 (4)	47 (8)	30 (11)	0.047	165 (7)

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; NA: not available.

countries (table 4). Over time, use of later-generation fluoroquinolones increased in all income groups. By 2013–2015, most patients in low-/lower-middle-income countries (100%), upper-middle-income countries (90%) and high-income countries (87%) were treated with later-generation fluoroquinolones (table 4).

Linezolid was more frequently prescribed in high-income countries (26%) than in low-/lower-middle-income (4%) and upper-middle-income (11%) countries (table 4). As with later-generation fluoroquinolones, use of linezolid has increased over time in all income groups. Although the introduction of linezolid occurred last in upper-middle-income countries, treatment of patients with linezolid in these countries in 2013–2015 was more common (44%) than in low-/lower-middle-income countries (34%), but less common than in high-income countries (54%) (table 4).

TABLE 2 Previous treatment history of 9036 patients with multidrug-resistant/rifampin-resistant tuberculosis

	Period 1 2001–2003	Period 2 2004–2006	Period 3 2007–2009	Period 4 2010–2012	Period 5 2013–2015	p-value trend over time	Total 2001–2015
None							
Total	270 (20)	451 (24)	563 (21)	440 (26)	373 (33)	<0.001	2097 (24)
Low-/lower-middle	6 (3)	29 (5)	99 (12)	109 (14)	6 (5)	<0.001	249 (10)
Upper-middle	190 (18)	60 (11)	156 (14)	22 (7)	230 (32)	<0.001	658 (17)
High	74 (54)	362 (48)	308 (44)	309 (52)	137 (49)	0.99	1190 (48)
Treated with first-line drugs							
Total	1081 (80)	1468 (76)	2133 (79)	1268 (74)	752 (67)	<0.001	6702 (76)
Low-/lower-middle	172 (97)	587 (95)	756 (88)	680 (86)	123 (95)	<0.001	2318 (90)
Upper-middle	845 (82)	490 (89)	985 (86)	299 (93)	488 (68)	<0.001	3107 (83)
High	64 (46)	391 (52)	392 (56)	289 (48)	141 (51)	0.99	1277 (52)
Treated with second-line drugs							
Total	13 (3)	295 (16)	662 (26)	406 (26)	276 (26)	<0.001	1652 (22)
Low-/lower-middle	2 (1)	80 (13)	149 (17)	70 (9)	30 (23)	0.074	331 (13)
Upper-middle	0 (0)	82 (15)	371 (36)	210 (80)	176 (27)	<0.001	839 (31)
High	11 (9)	133 (21)	142 (23)	126 (24)	70 (27)	<0.001	482 (22)

Data are presented as n (%), unless otherwise stated.

TABLE 3 Drug-susceptibility patterns of 9036 patients with multidrug-resistant/rifampin-resistant tuberculosis (TB)

	Period 1 2001–2003	Period 2 2004–2006	Period 3 2007–2009	Period 4 2010–2012	Period 5 2013–2015	p-value trend over time	Total 2001–2015
Resistance to fluoroquinolone							
Total	74 (5)	269 (15)	894 (34)	506 (31)	369 (31)	<0.001	2112 (24)
Low-/lower-middle	40 (25)	83 (14)	150 (18)	204 (27)	51 (39)	<0.001	528 (21)
Upper-middle	17 (2)	75 (15)	596 (54)	101 (38)	223 (28)	<0.001	1012 (27)
High	17 (12)	111 (15)	148 (21)	201 (34)	95 (34)	<0.001	572 (23)
Resistance to second-line injectable drugs							
Total	65 (5)	340 (19)	1064 (40)	456 (28)	441 (37)	<0.001	2366 (27)
Low-/lower-middle	21 (13)	55 (9)	201 (24)	131 (17)	23 (18)	<0.001	431 (17)
Upper-middle	27 (3)	125 (25)	715 (65)	86 (32)	282 (36)	<0.001	1235 (33)
High	17 (12)	160 (21)	148 (21)	239 (40)	136 (49)	<0.001	700 (28)
Extensively drug-resistant TB							
Total	25 (2)	125 (7)	711 (27)	212 (13)	218 (18)	<0.001	1291 (15)
Low-/lower-middle	10 (6)	24 (4)	74 (9)	50 (7)	20 (15)	0.004	178 (7)
Upper-middle	9 (1)	61 (12)	577 (52)	58 (22)	136 (17)	<0.001	841 (23)
High	6 (4)	40 (5)	60 (9)	104 (18)	62 (22)	<0.001	272 (11)

Data are presented as n (%), unless otherwise stated.

Since 2010, the use of bedaquiline has increased rapidly in all countries, especially in upper-middle-income countries. Detailed patterns of other individual drug usage are shown in supplementary table S6.

During the study period, patients in the low-/low-middle and high-income countries were treated with a median of five drugs whereas individuals in the upper-middle-income countries were treated with an

TABLE 4 Drug usage patterns of 9036 patients with multidrug-resistant/rifampin-resistant tuberculosis

	Period 1 2001–2003	Period 2 2004–2006	Period 3 2007–2009	Period 4 2010–2012	Period 5 2013–2015	p-value trend over time	Total 2001–2015
Group A							
Later-generation fluoroquinolone							
Total	148 (11)	817 (42)	1474 (54)	1528 (87)	1117 (91)	<0.001	5084 (57)
Low-/lower-middle	21 (12)	281 (46)	662 (77)	827 (100)	131 (100)	<0.001	1922 (74)
Upper-middle	0 (0)	37 (7)	265 (23)	199 (62)	742 (90)	<0.001	1243 (32)
High	127 (91)	499 (64)	547 (77)	502 (84)	244 (87)	<0.001	1919 (77)
Linezolid							
Total	15 (1)	149 (8)	154 (6)	314 (18)	555 (45)	<0.001	1187 (13)
Low-/lower-middle	0 (0)	21 (3)	24 (3)	22 (3)	44 (34)	<0.001	111 (4)
Upper-middle	0 (0)	0 (0)	4 (0)	71 (22)	361 (44)	<0.001	436 (11)
High	15 (11)	128 (16)	126 (18)	221 (37)	150 (54)	<0.001	640 (26)
Bedaquiline							
Total	0 (0)	0 (0)	3 (0)	302 (17)	523 (43)	<0.001	828 (10)
Low-/lower-middle	0 (0)	0 (0)	0 (0)	8 (1)	13 (10)	<0.001	21 (1)
Upper-middle	0 (0)	0 (0)	0 (0)	242 (75)	426 (52)	<0.001	668 (17)
High	0 (0)	0 (0)	3 (0)	52 (9)	84 (30)	<0.001	139 (6)
Group B							
Clofazimine							
Total	29 (2)	56 (3)	269 (10)	189 (11)	405 (33)	<0.001	948 (11)
Low-/lower-middle	0 (0)	20 (3)	201 (23)	50 (6)	57 (44)	<0.001	328 (13)
Upper-middle	0 (0)	3 (1)	19 (2)	57 (18)	309 (38)	<0.001	388 (10)
High	29 (21)	33 (4)	49 (7)	82 (14)	39 (14)	<0.001	232 (9)
Cycloserine or terizidone							
Total	813 (59)	1464 (75)	2129 (78)	1533 (88)	1130 (92)	<0.001	7069 (78)
Low/lower-middle	148 (83)	535 (87)	831 (97)	814 (98)	127 (97)	<0.001	2455 (94)
Upper-middle	605 (57)	362 (65)	742 (63)	225 (70)	767 (94)	<0.001	2701 (69)
High	60 (43)	567 (73)	556 (79)	494 (83)	236 (85)	<0.001	1913 (77)

Data are presented as n (%), unless otherwise stated.

TABLE 5 Treatment patterns of 9036 patients with multidrug-resistant/rifampin-resistant tuberculosis

	Period 1 2001–2003	Period 2 2004–2006	Period 3 2007–2009	Period 4 2010–2012	Period 5 2013–2015	p-value trend over time	Total 2001–2015
Number of drugs used							
Total	4 (4–4)	5 (4–5)	5 (4–5)	5 (5–5)	5 (4–6)	<0.001	5 (4–5)
Low/lower-middle	4 (4–4)	4 (4–5)	5 (5–6)	5 (5–5)	5 (4–6)	<0.001	5 (4–5)
Upper-middle	4 (4–4)	5 (4–5)	5 (4–5)	6 (5–6)	5 (4–6)	<0.001	4 (4–5)
High	4 (4–5)	5 (4–5)	5 (4–5)	5 (4–5)	5 (5–6)	<0.001	5 (4–5)
Number of effective drugs used							
Total	4 (3–4)	4 (3–5)	4 (4–5)	4 (4–5)	5 (4–5)	<0.001	4 (4–5)
Low/lower-middle	4 (3–4)	4 (4–5)	4 (4–5)	4 (4–5)	4 (4–5)	<0.001	4 (4–5)
Upper-middle	4 (3–4)	4 (3–5)	4 (4–5)	5 (4–6)	5 (4–6)	<0.001	4 (4–5)
High	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (4–5)	<0.001	4 (3–5)
Treatment duration months							
Total	18.5 (13.5–22.6)	19.8 (15.6–24)	19.9 (12.9–24.1)	20.3 (16.3–24)	19.9 (15.5–23.9)	0.75	19.9 (14.8–24)
Low/lower-middle	19.4 (13.7–22.1)	19.4 (18–21.9)	20.2 (18–24)	22 (9.1–24)	24 (20.6–24.4)	<0.001	20 (16.8–24)
Upper-middle	NA	22.5 (14.8–25)	19.4 (9.2–24.6)	21.9 (18.2–24.3)	19.5 (15–23.1)	<0.001	20.2 (12.8–24.1)
High	18 (13.5–23.7)	19.8 (14.8–24)	20 (17.5–24)	19.1 (16.6–23.3)	19.3 (15.4–23)	0.93	19.5 (16–24)
Treatment duration in patients with treatment success months							
Total	19.7 (18.1–23.3)	21.9 (18.9–24.2)	22.5 (19.2–24.7)	21.7 (18.6–24)	21.1 (18.7–24)	0.75	21.7 (18.8–24.1)
Low/lower-middle	20.3 (19.1–22. 8)	20 (18.9–22.6)	21.6 (19.5–24.5)	24 (23.1–24.4)	24 (24–24.4)	<0.001	21.6 (19.4–24)
Upper-middle	NA	24.1 (22.3–26.4)	24 (20.9–26.1)	22.1 (19.4–24.1)	21 (18.8–23.9)	<0.001	23 (19.6–24.7)
High	18.1 (16.5–24)	22.3 (18.2–24)	21 (18.3–24.2)	20 (18–23.5)	20 (18–24)	0.93	20.5 (18–24)
Hospitalisation							
Total	1180 (88)	1015 (56)	1757 (65)	781 (68)	494 (69)	<0.001	5227 (68)
Low/lower-middle	26 (15)	73 (12)	521 (61)	242 (51)	63 (51)	<0.001	925 (41)
Upper-middle	1057 (100)	445 (80)	880 (75)	38 (42)	210 (60)	<0.001	2630 (81)
High	97 (95)	497 (77)	356 (54)	501 (85)	221 (94)	<0.001	1672 (75)
Surgical intervention							
Total	16 (7)	70 (4)	148 (7)	82 (8)	53 (8)	<0.001	369 (6)
Low/lower-middle	0 (0)	4 (1)	43 (6)	12 (3)	2 (3)	0.23	61 (3)
Upper-middle	NA	16 (3)	38 (5)	3 (4)	27 (8)	<0.001	84 (5)
High	16 (17)	50 (8)	67 (11)	67 (12)	24 (10)	0.13	224 (11)

Data are presented as median (interquartile range) or n (%), unless otherwise stated. NA: not available.

average of four drugs, with all three groups treated with an average of four effective anti-TB drugs (IQR 4–5) (table 5). Total treatment duration in patients who achieved treatment success was the longest in upper-middle-income countries (median 23 months, IQR 19.6–24.7 months), although it declined from 24.1 months (IQR 22.3–26.4 months) to 21 months (IQR 18.8–24.7 months) over time (p<0.001). Surgical resection was more common in high-income countries (11%) than in low-/lower-middle-income countries (3%) and upper-middle-income countries (5%) (table 5).

Treatment outcomes

Over the study period, treatment outcomes improved over time in all income groups. Overall, treatment success rates were highest in high-income countries and lowest in upper-middle-income countries. Deaths were more common among patients in upper-middle-income countries (32%) than in low-/lower-middle-income countries (17%) and high-income countries (8%) (p<0.001). While the proportion of patients who died decreased over time in upper-middle- and high-income countries, this proportion remained unchanged in low-/lower-middle-income countries (table 6).

The adjusted odds ratio (aOR) for treatment success *versus* all poor outcomes by income group (with upper-middle-income countries (the income group with the worst treatment outcomes) taken as reference) is provided in table 7. After adjusting for demographic factors, radiographic features, drug susceptibility patterns and use of group A drugs (model 5), the odds of treatment success were higher in low-/low-middle-income countries than in upper-middle-income countries (aOR 1.9, 95% CI 1.26–2.85) between 2001 and 2003, until 2007–2009 and thereafter there was no difference. The odds of treatment success in high-income countries were higher than those in upper-middle-income countries during the study periods (table 7).

The odds of death (*versus* all other outcomes) did not differ between patients in low-/low-middle-income countries and those in upper-middle-income countries over time except for the 2007–2009 period.

TABLE 6 Treatment outcomes of 9036 patients with multidrug-resistant/rifampin-resistant tuberculosis

	Period 1 2001–2003	Period 2 2004–2006	Period 3 2007–2009	Period 4 2010–2012	Period 5 2013–2015	p-value trend over time	Total 2001–2015
Treatment success							
Total	636 (46)	1238 (64)	1417 (52)	1215 (69)	880 (72)	<0.001	5386 (60)
Low-/lower-middle	107 (60)	415 (67)	501 (58)	551 (66)	102 (78)	0.048	1676 (64)
Upper-middle	427 (40)	302 (54)	392 (33)	203 (63)	552 (67)	<0.001	1876 (48)
High	102 (73)	521 (67)	524 (74)	461 (77)	226 (81)	<0.001	1834 (73)
Treatment failure or relapse							
Total	208 (25)	103 (8)	233 (14)	181 (13)	42 (5)	<0.001	767 (13)
Low-/lower-middle	16 (13)	18 (4)	57 (10)	81 (10)	5 (5)	0.06	177 (10)
Upper-middle	188 (31)	38 (11)	131 (25)	49 (19)	31 (5)	<0.001	437 (19)
High	4 (4)	47 (8)	45 (8)	51 (10)	6 (3)	0.59	153 (8)
Loss to follow-up or transfer							
Total	248 (18)	345 (18)	459 (17)	179 (10)	155 (13)	<0.001	1386 (15)
Low-/lower-middle	34 (19)	106 (17)	195 (23)	81 (10)	6 (5)	<0.001	422 (16)
Upper-middle	196 (19)	96 (17)	180 (15)	46 (14)	116 (4)	0.004	634 (16)
High	18 (13)	143 (18)	84 (12)	52 (9)	33 (12)	<0.001	330 (13)
Death							
Total	229 (26)	254 (17)	595 (30)	170 (12)	135 (13)	<0.001	1383 (21)
Low-/lower-middle	21 (16)	77 (16)	104 (17)	116 (17)	17 (14)	0.77	335 (17)
Upper-middle	194 (31)	119 (28)	456 (54)	24 (11)	104 (16)	<0.001	897 (32)
High	14 (12)	58 (10)	35 (6)	30 (6)	14 (6)	0.002	151 (8)

Data are presented as n (%), unless otherwise stated.

Meanwhile, the probability of mortality was generally lower among patients in high-income countries than among patients in upper-middle-income countries during the study periods (supplementary table S7).

Discussion

In this study, we analysed data on 9036 patients with MDR/RR-TB treated between 2001 and 2015 according to national income levels. Over the period studied, MDR/RR-TB treatment outcomes improved over time in all patients despite the growing prevalence of resistance to fluoroquinolones and second-line

TABLE 7 Odds ratios for treatment success by income category (relative to upper-middle-income countries) over time, using imputed data

	Period 1 2001–2003	Period 2 2004–2006	Period 3 2007–2009	Period 4 2010–2012	Period 5 2013–2015
Model 1 (unadjusted)					
Low/lower-middle	2.22 (1.61–3.07)	2.01 (1.36–2.97)	2.34 (1.75–3.13)	1.24 (0.57–2.7)	1.3 (0.51–3.3)
High	4.07 (2.74–6.04)	1.24 (0.89–1.71)	2.59 (1.75–3.83)	3.22 (1.61–6.45)	2.5 (1.34–4.65)
Model 2					
Low/lower-middle	1.78 (1.26–2.53)	1.86 (1.22–2.84)	2.41 (1.77–3.29)	1.4 (0.65–3.02)	1.32 (0.52–3.34)
High	3.4 (2.25–5.14)	1.11 (0.77–1.59)	2.56 (1.71–3.82)	3.46 (1.74–6.87)	2.54 (1.36–4.74)
Model 3					
Low/lower-middle	1.7 (1.16–2.48)	2.07 (1.35–3.19)	2.73 (1.99–3.76)	1.33 (0.6–2.97)	1.17 (0.42–3.25)
High	3.45 (2.24–5.32)	1.19 (0.8–1.76)	2.28 (1.51–3.44)	2.85 (1.4–5.8)	2.32 (1.2–4.48)
Model 4					
Low/lower-middle	1.91 (1.27–2.87)	2.03 (1.31–3.16)	2.23 (1.59–3.11)	1.21 (0.53–2.74)	1.32 (0.48–3.63)
High	3.6 (2.27–5.71)	1.4 (0.96–2.05)	2.17 (1.45–3.24)	2.62 (1.28–5.37)	2.3 (1.2–4.42)
Model 5					
Low/lower-middle	1.9 (1.26–2.85)	2.05 (1.29–3.25)	1.94 (1.36–2.75)	1.13 (0.49–2.61)	1.39 (0.45–4.24)
High	2.94 (1.78–4.84)	1.44 (0.98–2.11)	2.14 (1.47–3.11)	2.53 (1.24–5.19)	2.3 (1.18–4.49)

Data are presented as OR (95% CI). Model 2: adjusted for age, sex, body mass index, smoking, HIV infection and diabetes mellitus; model 3: model 2 + adjustment for previous tuberculosis treatment, acid-fast bacilli smear and radiographic severity; model 4: model 3 + adjustment for susceptibility to frequently used drugs, second-line injectable drugs and fluoroquinolones; model 5: model 4 + adjustment for the number of group A drugs used (adjusting two or more group A drugs used *versus* fewer than two group A drugs used).

injectable drugs. Overall, the treatment success rate was best in high-income countries (73%), followed by low-/lower-middle-income (64%) and then upper-middle-income (48%) countries. The probability of treatment success in upper-middle-income countries was lower than that in low-/lower-middle-income countries during the early study period, but was not different starting in 2010. However, treatment success was higher in high-income countries compared to upper-middle income countries throughout the study period.

MDR/RR-TB patients in upper-middle-income countries had lower treatment success and there are plausible reasons for this finding. Indeed, the MDR/RR-TB patients in the upper-middle-income countries had a higher prevalence of HIV infection, lower use of antiretroviral therapy, more cigarette smoking and presented with more advanced disease (presence of cavity and bilateral involvement) compared to patients in other countries. In addition, resistance to pyrazinamide, second-line injectable drugs and/or fluoroquinolones (the latter two reflected by greater numbers of extensively drug-resistant TB patients) were more commonly associated with patients in the upper-middle-income countries. HIV infection [23], presence of cavities [24] and additional drug resistance [25, 26] have all been reported as poor prognostic factors for MDR-TB patients. These may have contributed to the worse treatment outcomes observed in upper-middle-income countries.

Limited use of group A drugs may have also played a part in the worse outcomes observed among patients in upper-middle-income countries. During the earlier years of the study, later-generation fluoroquinolones were used much less commonly in these countries. During the 2001–2003 period, no patients received later-generation fluoroquinolones in upper-middle-income countries, whereas 12% of patients in low-/lower-middle-income countries and 91% of patients in high-income countries received these drugs. Furthermore, linezolid was introduced in upper-middle-income countries in 2008, long after its introduction in high-income (2001) and low-/lower-middle-income (2004) countries. Finally, access to newer drugs has in some cases been better in low-/lower-middle-income countries. For example, collaborations between the private and public sectors have enabled access to later-generation fluoroquinolones in Tanzania, Uganda and Zambia [27, 28]. Similarly, approval of a generic version of linezolid in the early 2000s facilitated access to this drug in India, whereas the patent for linezolid was retained until 2014 in South Africa, an upper-middle-income country [29, 30]. Finally, disbursements by the Global Fund to Fight AIDS, Tuberculosis and Malaria have been primarily concentrated in low-/lower-middle-income countries. Currently, the 10 countries that have benefited most from the Global Fund were all low-/lower-middle-income, except China [31].

Beginning in 2010, MDR/RR-TB treatment outcomes improved in upper-middle-income countries. The treatment success rate was 33% during the 2007–2009 period, but increased to 63% during the 2010–2012 period in these countries. Comparing the same periods, increased use of group A drugs occurred in upper-middle-income countries. Increased use of new and repurposed anti-TB drugs may have resulted in the improved treatment outcomes observed in upper-middle-income countries.

Although the probability of treatment success in upper-middle-income countries was lower than that in low-/lower-middle-income countries between 2001 and 2009, there was no difference from 2010 to 2015. However, the gap between upper-middle- and high-income countries persists even after adjusting for use of group A drugs. In low-income and middle-income countries, access to healthcare does not guarantee adequate treatment for diseases such as TB [32]. Only 13–45% of TB patients were correctly managed in these countries [32]. Untrained primary care providers or inadequate supervisory support could result in low quality of care in resource-poor settings [33]. In high-income countries, comprehensive and patient-centred approaches for TB patients, electronic device-based adherence monitoring [34], psychosocial interventions, social worker assistance and financial support [35, 36] may have contributed to improved treatment outcomes. In addition, the better overall healthcare systems of high-income countries may have played a role in improved treatment outcomes. Although improvements in personal healthcare access and quality have been observed globally over the past 25 years, these attainments have been slower to take hold in southern sub-Saharan Africa and south Asia, where TB is most prevalent [37].

To best interpret these results, it is important to consider the limitations of our study. First, the data analysed in this study were obtained from published or "to be published" articles rather than from nationwide reporting systems. Consequently, the results could have been affected by selection bias. Different proportions of patients from different countries were included in each period. This could cause fluctuations in several variables over the periods. For example, the fluctuating frequency of HIV co-infection in upper-middle-income countries was driven by different number of patients for each period from South Africa, the country with the highest burden of HIV infection in the world [38]. Second, the role of wealth inequality, which also affects TB incidence and prevalence [39, 40] could not be investigated in this study. Even in high-income countries, impoverished populations are at higher risk of TB [41] and such inequality

may affect TB mortality within a country [42]. Third, the impact of healthcare systems and policies in each country could not be considered in this study. Different health policies could result in different TB treatment modalities and outcomes, even in countries with similar income levels [38, 43]. Despite these limitations, to our knowledge ours is the first study to use extensive patient data (representative >9000 patients with MDR/RR-TB) to assess changes in demographic factors, disease severity, drug susceptibility patterns, treatment modalities and treatment outcomes according to national income levels and over time.

In summary, treatment outcomes for patients with MDR/RR-TB have improved in all income groups, which in part reflects the effectiveness of group A drugs that have become widely available in recent years. Despite these improvements, treatment outcomes, especially in upper-middle-income countries, remain unsatisfactory. Greater investment in diagnosis, treatment, and support for MDR/RR-TB patients is urgently needed.

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