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ORIGINAL ARTICLE

Treatment Outcomes Among Pediatric Patients With Highly Drug-Resistant Tuberculosis: The Role of New and Repurposed Second-Line Tuberculosis Drugs

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Background. Among pediatric patients with multidrug-resistant tuberculosis (MDR-TB), limited data exist regarding treatment outcomes in the context of the new and repurposed second-line TB drugs (SLDs). We aimed to describe the treatment outcomes among pediatric MDR-TB patients receiving new and repurposed SLDs including the proportion who achieved favorable outcomes.

Methods. We conducted a retrospective cohort study among pediatric patients (age ≤18 years) treated for MDR-TB in the country of Georgia from 2009 to 2016. A "new and repurposed" SLD regimen was defined as a regimen that included linezolid, bedaquiline, and/or delamanid. Favorable treatment outcome was defined by treatment completion or documented microbial "cure" status at the end of treatment. We assessed the association between the use of the new and repurposed SLDs with MDR-TB treatment outcomes using bivariate analyses and log-binomial regression.

Results. There were 124 pediatric MDR-TB patients (median age: 13.7; interquartile range: 4.6-16.0) initiating treatment; 119 (96.0%) had a treatment outcome recorded and were included in our analyses. Eighteen (15.1%) patients received new and repurposed SLDs from 2015 or later. After adjusting for potential confounders, the proportion achieving favorable MDR-TB treatment outcomes was higher among patients treated with SLD regimens that included new and/or repurposed drugs when compared with those treated without (adjusted risk ratio: 1.17; 95% confidence interval: 0.51-2.72).

Conclusions. We observed a high proportion of favorable treatment outcomes among pediatric patients with MDR-TB receiving the new and repurposed SLDs. Further studies to evaluate the efficacy and children's tolerability of the new and repurposed SLDs are still warranted.

Key words. bedaquiline; delamanid; linezolid; pediatric MDR-TB; treatment outcome.

The World Health Organization (WHO) estimated that there were 10 million new tuberculosis (TB) cases in 2018 including 1.1 million pediatric TB cases (~11%) [1]. Importantly, the emergence of drug-resistant TB threatens the recent progress toward achieving the End TB Strategy's goals [2]. In 2018, there were approximately half a million new cases of rifampicin (RIF)-resistant TB of which 78% were multidrug-resistant TB (MDR-TB) cases [1]. Pediatric MDR-TB remains a public health emergency with an estimated 33 000 new pediatric MDR-TB cases reported in 2018 [3–6]. Furthermore, the large majority of pediatric MDR-TB cases are due to primary transmission [7] resulting from the ongoing transmission of MDR-TB and indicating existing challenges with identifying, reporting, and managing household pediatric contacts of MDR-TB patients [8, 9].

The management and treatment of pediatric MDR-TB are complex, in part because obtaining a definitive microbial diagnosis is difficult, especially among patients aged less than 5 years [10]. Without culture confirmation and direct detection of drug resistance, clinicians cannot prescribe the most effective anti-TB drugs regimens [11]. Currently available treatment guidelines for pediatric MDR-TB cases are also mostly extrapolated from studies conducted among adult MDR-TB populations [12], including recommendations to incorporate novel and repurposed second-line TB drugs (ie, bedaquiline, delamanid, and linezolid) into the pediatric MDR-TB treatment regimens. The use of new and repurposed second-line TB drugs ("new and repurposed SLDs") among children, adolescents, and adults was first incorporated into the WHO

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treatment guidelines in 2016 [13, 14]. However, to date, studies assessing the use of these new and repurposed SLDs among pediatric patients are limited to case reports and reports from compassionate use programs [5, 15–18].

Children typically have a high TB treatment success rate [19]; however, the mortality rate among pediatric MDR-TB patients remains high (11%) [19] and is similar compared with adult MDR-TB patients (13%) [20]. Among adults with MDR-TB, the use of bedaquiline, delamanid, and linezolid has been associated with higher overall cure rates [21–25], but there are limited data among pediatric MDR-TB patients. Additionally, the new and repurposed SLDs may lead to various complications such as corrected QT interval (QTc) prolongation and peripheral neuropathy [6]. However, adverse drug reactions associated with these new and repurposed SLDs are not well described among pediatric patients with MDR-TB. To generate evidence-based approaches to clinical management of pediatric MDR-TB, there is an urgent need to investigate the use of the new and repurposed SLDs among children. Given existing gaps in knowledge, the purpose of our study was to assess the final MDR-TB treatment outcomes among pediatric patients with MDR-TB treated with new and repurposed SLDs compared with those treated with the traditional SLDs treatment regimens. A secondary objective was to describe the frequency of adverse events (AEs) among these pediatric patients receiving SLD regimens.

METHODS

Setting and Study Design

We conducted a retrospective cohort study among pediatric patients (≤18 years) treated for MDR-TB in the country of Georgia from 2009 to 2016. Eligible participants included bacteriologically confirmed and clinically diagnosed pediatric MDR-TB [26] patients reported to Georgia National Center for Tuberculosis and Lung Diseases (NCTLD) TB surveillance system. Bacteriologically confirmed cases [26] were treated based on the drug susceptibility test (DST) results, whereas clinically confirmed cases [26] were treated according to DST results of the index case. In Georgia, delamanid and linezolid were prescribed for pediatric patients with MDR-TB beginning in 2015. Bedaquiline was incorporated into the treatment regimens for pediatric patients with MDR-TB starting in 2016. The dosage used for these 3 new and repurposed TB drugs (ie, linezolid, delamanid, and bedaquiline) followed WHO's treatment guidelines [27] (Supplementary Table 1). Per Georgian TB treatment guidelines, all pediatric patients (ie, clinically diagnosed or bacteriologically confirmed) with MDR-TB are required to be hospitalized until their culture converted to negative (for bacteriologically confirmed patients) or until patients showed clinical improvements (for clinically diagnosed patients) [28].

Definitions

The primary exposure for this study was the type of MDR-TB treatment, defined dichotomously as either new and repurposed SLDs or traditional SLDs. A treatment regimen containing either bedaquiline, delamanid, and/or linezolid was categorized as a new and repurposed SLDs regimen. Treatment regimens without bedaquiline, delamanid, or linezolid were categorized as "traditional SLDs" regimens. The primary outcome for this study was the final MDR-TB treatment outcome recorded in NCTLD's surveillance system. Following WHO guidelines [29], patients who were cured and those who successfully completed treatment were defined to have favorable outcomes. Patients who died, were lost to follow-up, or in whom MDR TB treatment failed (ie, sputum culture remained positive after 5 months post-MDR-TB treatment initiation) were defined as having a poor outcome.

We also reported the incidence of AEs during MDR-TB treatment. AEs were defined based on medical record abstraction. Electrocardiography (ECG) was performed only among pediatric patients receiving bedaquiline, delamanid, moxifloxacin, or clofazimine to monitor QTc prolongation. Following Georgia's TB treatment guideline, we determined QTc prolongation using Fridericia's correction formula with QTc > 450 ms considered "prolonged" [30]. Before 2016, the severity of AEs was classified by pediatricians according to Georgian TB Treatment guidelines. Since 2016, the severity of AEs was assessed and classified according to the Division of Microbiology and Infectious Diseases (DMID) pediatric toxicity tables [31] and Common Terminology Criteria for Adverse Events (CTCAE) [32].

Demographic (eg, age, gender, and nationality) and clinical characteristics (eg, MDR-TB treatment information, laboratory results, and history of MDR-TB-associated surgery during treatment) were abstracted from medical charts. DST results used to determine treatment regimen were classified as "patient DST" if sputum sample was available and DST was successfully performed, otherwise the patient was treated according to DST results of the index case (ie, "DST index case"). Human immunodeficiency virus (HIV) status was obtained from NCTLD surveillance records. Body mass index (BMI) was expressed in *z*-scores calculated with the λ-median-coefficient of variation (LMS) method following the US Centers for Disease Control and Prevention (CDC)'s growth charts with smoothed percentiles for children, adolescents, and young adults aged 2 to 20 years [33] and categorized according to the WHO Child Growth Standards [34, 35].

Statistical Analyses

Fisher's exact or Chi-square tests were performed to assess the bivariate association between categorical demographic/clinical predictors and study outcomes (ie, AEs and final MDR-TB treatment outcomes). Wilcoxon rank-sum tests were performed to assess the bivariate association between continuous

variables and final MDR-TB treatment outcomes. Univariate and multivariable log-binomial logistic regression models were used to estimate the crude and adjusted risk ratios (aRRs) of favorable MDR-TB treatment comparing pediatric patients treated with the new and repurposed SLDs vs traditional SLDs. Covariate selection for the multivariable log-binomial logistic regression model was based on the observed bivariate associations, directed acyclic graph theory, and factors identified in the previously published literature. Sensitivity analyses were performed to assess how the primary measure of association (ie, risk ratio) differed when clofazimine, amoxicillin/clavulanate, and clarithromycin were included in the new and repurposed SLDs definition.

Institutional Review Board Approval

This study was approved by the Institutional Review Board (IRB) at the NCTLD in Georgia.

RESULTS

Study Population and Baseline Characteristics

During the study period, there were 124 pediatric patients treated with second-line anti TB drugs reported to the NCTLD, and 18 (14.9%) of whom had extensively drug-resistant TB (XDR-TB) [26, 36] (Table 1). The majority of pediatric patients in our cohort were male (75/124, 60.5%) and Georgian (111/124, 90.2%). The proportion of patients with bacteriological confirmation at baseline was 51.6% (64/124). Compared with clinically diagnosed patients, patients with bacteriological confirmation were older and more likely to have an abnormal chest X-ray ($P < .05$) (Supplementary Table 2).

New and repurposed SLDs were prescribed among 19 of 124 patients (15.3%). Among these, 18 (94.7%) had linezolid-containing regimens, 11 (57.9%) received delamanid, and 3 (15.8%) received bedaquiline (Table 2). Of the 19 (10.5%) pediatric MDR-TB patients, 2 patients received all 3 of the new and repurposed SLDs. Among those who received the new and repurposed SLDs, the median time from the TB treatment initiation to the start of a new or repurposed drug was 5.2 months (interquartile range [IQR]: 1.6-8.9). The median duration of patients receiving linezolid was 11.8 months (IQR: 8.6-17.5), 6.4 months (IQR: 5.7-13.5) for bedaquiline, and 5.6 months (IQR: 5.5-6.1) for delamanid. Pyrazinamide, ethambutol, prothionamide, kanamycin, para-aminosalicylic acid, cycloserine, and capreomycin were the most common companion drugs prescribed in both new and repurposed SLDs and traditional SLDs groups (Supplementary Table 3). Levofloxacin prescription was more common among patients treated with the traditional SLDs (95.2%) compared with those treated with the new and repurposed SLDs (77.8%) ($P = .02$). Moxifloxacin, however, was more commonly prescribed among patients treated with the new and repurposed SLDs (72.2%) compared with those treated with the traditional SLDs (11.9%) ($P < .01$). The MDR-TB treatment duration was similar among patients treated with new and repurposed vs traditional SLDs with a median of 20 months (Table 1).

Among 124 MDR-TB pediatric patients, a total of 119 (96.0%) had final treatment outcomes reported and were included in final analyses (Table 3). Among patients included in final analyses, 18 (18/119, 15.1%) received treatment regimens that included the new and repurposed SLDs, while the remaining 101 (101/119, 84.9%) received the traditional SLD regimens. More than half (65/119, 54.6%) of pediatric MDR-TB patients included in the final analyses had DST results available. Fifty-six (47.1%) clinical cases in our cohort were presumed to have and treated for MDR-TB based on the DST results of the index case.

Factors Associated With Favorable Final MDR-TB Treatment Outcomes

Overall, 98 (82.3%) of the 119 pediatric MDR-TB patients had a favorable final treatment outcome and 21 (17.7%) had an unfavorable outcome including 2 deaths (Table 3). Among 18 patients treated with regimens that included the new and repurposed SLDs, 17 (94.4%) had a favorable treatment outcome, whereas 81 (80.2%) patients treated with the traditional SLDs had a favorable treatment outcome (proportion difference = 14.2%; 95% confidence interval [CI]: 1.12-27.37). The one patient with poor treatment outcome in the new and repurposed SLDs group was lost to follow-up after 7 months of treatment.

In the unadjusted model, the proportion of favorable MDR-TB treatment outcomes among patients treated with the new and repurposed SLDs was modestly higher when compared with the proportion among those who were treated with the traditional SLDs (crude risk ratio [cRR]: 1.18; 95% CI: 1.02-1.37). Male patients had significantly lower proportion of favorable MDR-TB treatment outcomes (77.0%) compared with female patients (91.1%) (cRR: 0.85; 95% CI: 0.72-0.99). The proportion with favorable treatment outcomes was similar between pediatric patients who were bacteriologically confirmed (82.5%) compared with patients who were clinically diagnosed (82.1%) (cRR: 1.00; 95% CI: 0.84-1.18).

In a multivariable model adjusted for age, baseline sputum culture results, drug-resistance type, TB disease site, and surgery, the proportion of patients with favorable treatment outcomes among those treated with new and repurposed SLDs remained modestly (but nonsignificantly) higher compared with those treated with traditional SLDs (aRR: 1.17; 95% CI: 0.51-2.72). Age, baseline sputum culture results, drug-resistance type, TB disease site, and surgery were not predictive of favorable MDR-TB treatment outcome in the same multivariable model. The unadjusted (cRR: 1.16; 95% CI: 1.00-1.35) and adjusted risk ratios (aRR: 1.10; 95% CI: 0.54-2.22) for favorable MDR-TB treatment outcomes were similar when clofazimine, amoxicillin/clavulanate, and clarithromycin were included in the new and repurposed SLDs definition (Supplementary Table 4).

Table 1. Patients' Demographic, Clinical Characteristics, and Treatment Outcomes by the Type of Regimen Received Among Pediatric Patients With Multidrug-Resistant Tuberculosis in the Country of Georgia, 2009–2016 (N = 124)

Characteristics	Drug Regimen: Traditional SLDs N (%) = 105 (84.7%) n (%)	Drug Regimen: New and Repurposed SLDs[a] N (%) = 19 (15.3%) n (%)	Total N = 124	*P*-value[b]
Demographic				
Age, median (IQR)	12.3 (4.0-15.8)	15.3 (13.9-16.6)	13.7 (4.6-16.0)	**.02**[c]
Age group				
0-5	31 (29.5)	3 (15.8)	34 (27.4)	**.04**[d]
6-10	16 (15.2)	0 (0.0)	16 (12.9)	
11-15	36 (34.3)	7 (36.8)	43 (34.7)	
16-18	22 (21.0)	9 (47.4)	31 (25.0)	
Gender				
Female	40 (38.1)	9 (47.4)	49 (39.5)	.45
Male	65 (61.9)	10 (52.6)	75 (60.5)	
Nationality				
Georgian	93 (89.4)	18 (94.7)	111 (90.2)	.69[d]
Other[e]	11 (10.6)	1 (5.3)	12 (9.8)	
Comorbidities				
HIV Status				
Negative	43 (41.0)	19 (100.0)	62 (50.0)	**<.01**[d]
Positive	1 (1.0)	0 (0.0)	1 (0.8)	
Unknown	61 (58.1)	0 (0.0)	61 (49.2)	
Baseline clinical information				
Baseline smear				
Negative	28 (32.6)	13 (72.2)	41 (39.42)	**<.01**
Positive	58 (67.4)	5 (27.8)	63 (60.6)	
Missing	19	1	20	
Baseline culture				
Negative	41 (47.1)	1 (5.9)	42 (40.4)	**<.01**
Positive	46 (52.9)	16 (91.2)	62 (59.6)	
Missing	18	2	20	
Baseline chest findings				
Normal	58 (55.2)	4 (21.0)	62 (50.0)	**.01**
Abnormal CXR reading	47 (44.8)	15 (79.0)	62 (50.0)	
Cavitary				
No	100 (95.2)	17 (89.5)	117 (94.4)	.29[d]
Yes	5 (4.8)	2 (10.5)	7 (5.7)	
Pulmonary infiltration				
No	71 (67.6)	8 (42.1)	79 (63.7)	**.04**
Yes	34 (32.4)	11 (57.9)	45 (36.3)	
Fibrosis				
No	87 (82.9)	13 (68.4)	100 (80.7)	.21[d]
Yes	18 (17.1)	6 (31.6)	24 (19.4)	
BMI, kg/m^2, median (IQR) (n = 92)	19.4 (17.4-22.0)	18.7 (17.3-20.5)	19.1 (17.4-21.8)	
BMI *z*-score (BMI*z*) classification (n = 83)[f]				
Underweight (BMI*z* < –2.00)	5 (7.7)	1 (5.6)	6 (7.2)	.35[c]
Normal (BMI*z* –2.00 to 2.00)	55 (84.6)	17 (94.4)	72 (86.8)	
Overweight/obese (BMI*z* > 2.00)	5 (7.7)	0 (0.0)	5 (6.0)	
Missing	40	1	41	
TB treatment information				
Case definition				
Newly diagnosed patients	95 (90.5)	19 (100.0)	114 (91.9)	.45[d]
Relapse	9 (8.6)	0 (0.0)	9 (7.3)	
Treatment after failure	1 (1.0)	0 (0.0)	1 (0.8)	
TB diagnosis type				
Bacteriologically confirmed	48 (45.7)	16 (84.2)	64 (51.6)	**<.01**
Clinically diagnosed	57 (54.3)	3 (15.8)	60 (48.4)	

Table 1. Continued

Characteristics	Drug Regimen: Traditional SLDs N (%) = 105 (84.7%) n (%)	Drug Regimen: New and Repurposed SLDs[a] N (%) = 19 (15.3%) n (%)	Total N = 124	*P*-value[b]
TB disease site				
Pulmonary disease[g]	41 (39.1)	16 (84.2)	57 (46.0)	**<.01**
Extrapulmonary disease	64 (61.0)	3 (15.8)	67 (54.0)	
Treatment duration (month), median (IQR)	20.2 (15.8-22.6)	20.2 (20.0-20.6)	20.2 (16.4-22.4)	.70[c]
Number of hospitalization				
1	70 (69.3)	7 (38.9)	77 (64.7)	**.01**
>1	31 (30.7)	11 (61.1)	42 (35.3)	
Duration of first hospitalization in days, median (IQR)	39 (31-65)	36 (22-61)	39 (29-65)	.68[c]
Adjuvant surgery				
No	89 (89.9)	15 (79.0)	104 (88.1)	.24[d]
Yes	10 (10.1)	4 (21.1)	14 (11.9)	
Segmentectomy	6	0	6	
Lobectomy	1	4	5	
Other	3	0	3	
DST information				
DST results used to determine treatment regimen				
Patients' DST	53 (50.5)	16 (84.2)	69 (55.7)	**.01**
Index Case DST	52 (49.5)	3 (15.8)	55 (44.4)	
Drug resistance type				
RR/MDR TB	68 (66.0)	4 (22.2)	72 (59.5)	**<.01**
Pre-XDR-TB	23 (22.3)	8 (44.4)	31 (25.6)	
XDR-TB	12 (11.7)	6 (33.3)	18 (14.9)	
Missing	2	1	3	
DST profile				
Isoniazid resistance, n = 119	97 (97.0)	19 (100.0)	116 (97.5)	1.00[d]
Rifampicin resistance, n = 121	100 (97.1)	18 (100.0)	118 (97.5)	1.00[d]
Streptomycin resistance, n = 116	92 (94.9)	19 (100.0)	111 (95.7)	.59[d]
Ethambutol resistance, n = 113	77 (81.9)	17 (89.5)	94 (83.2)	.52[d]
Pyrazinamide resistance, n = 104	18 (20.7)	8 (47.1)	26 (25.0)	**.03**[d]
Kanamycin resistance, n = 97	27 (33.3)	9 (56.3)	36 (37.1)	.08
Ofloxacin resistance, n = 96	16 (20.0)	11 (68.8)	27 (28.1)	**<.01**[d]
Protionamide resistance, n = 95	51 (63.0)	1 (7.1)	52 (54.7)	**<.01**
Capreomycin resistance, n = 94	12 (15.0)	2 (14.3)	14 (14.9)	1.00[d]
PAS resistance, n = 93	9 (11.4)	4 (28.6)	13 (14.0)	.10[d]
Treatment outcome				
Cured	24 (22.9)	14 (73.7)	38 (30.7)	**<.01**[d]
Treatment completed	57 (54.3)	3 (15.8)	60 (48.4)	
Treatment failed	1 (1.0)	0 (0.0)	1 (0.8)	
Lost to follow-up	17 (16.2)	1 (5.3)	18 (14.5)	
Died	2 (1.9)	0 (0.0)	2 (1.6)	
Transferred care[h]	2 (1.9)	0 (0.0)	2 (1.6)	
Outcome unknown/missing	2 (1.9)	1 (5.3)	3 (2.4)	

Bold values indicate that the finding is statistically significant at level of confidence of 5% (2-sided *P*-value < .05).
Abbreviations: BMI, body mass index; CXR, chest X-ray; DST, drug susceptibility test; HIV, human immunodeficiency virus; IQR, interquartile range; PAS, para-aminosalicylic acid; TB, tuberculosis.
[a]Patients received bedaquiline-, delamanid-, or linezolid-containing regimen.
[b]*P*-values obtained from Chi-square tests unless indicated otherwise.
[c]*P*-values obtained from Wilcoxon rank-sum tests.
[d]*P*-values obtained from Fisher's exact tests.
[e]Other nationality included 5 Azeris and 7 Russians.
[f]BMI *z*-scores were calculated only among patients aged 2-18 years old.
[g]Included patients with both pulmonary and extrapulmonary.
[h]Patients transferred outside of Georgia to continue treatment.

Adverse Events

Any AE during the course of MDR-TB treatment was reported by 79% (94 of 119) of pediatric patients (Table 4). The most common AEs reported among pediatric MDR-TB patients in our cohort included nausea (53.9%), joint pain/arthralgia (24.4%), anxiety (18.5%), gastrointestinal tract disturbance

Table 2. Resistance Profile and Drug Regimen Prescription Among Patients Receiving New and Repurposed Second-Line TB Drugs, Georgia 2009–2016 (N = 19)

Cases	Age (years)	Sex	DST[a]	Sputum Smear at Baseline	Resistance pattern (In Addition to INH, RIF, and STM)	Drug Regimen Received	Treatment Duration (months)	Final Treatment Outcomes
1	17	F	Patient DST	Positive	EMB KM OFX	PZA PTO CPM CYS CFZ **LZD BDQ DLM**	21	Cured
2	15	M	Patient DST	Positive	EMB KM CPM PAS	PZA EMB CPM LFX CYS PAS CFZ **LZD**	20	Treatment Completed
3	16	M	Index Case DST	Negative	KM OFX	PZA EMB CPM MFX CYS PAS CFZ **LZD**	7	Lost to follow-up
4	15	M	Patient DST	Negative	EMB KM OFX	PZA PTO SPM LFX MFX CYS PAS AMC CFZ **LZD DLM** IMI/CIS	24	Cured
5	1	M	Index Case DST	Missing	EMB PZA KM OFX	PZA CPM MFX CYS PAS CFZ **LZD**	20	Treatment Completed
6	4	F	Index Case DST	Negative	EMB PZA KM OFX	PZA CPM MFX CYX PAS CFZ **LZD**	20	Treatment Completed
7	14	F	Patient DST	Positive	EMB PZA KM PAS	PZA EMB PTO CPM LFX CYS PAS **LZD DLM**	20	Cured
8	16	M	Patient DST	Positive	EMB KM PTO PAS	PZA EMB CPM LFX CYS CFZ **LZD DLM**	20	Cured
9	16	F	Patient DST	Positive	EMB	PZA EMB CPM MFX CYS PAS **LZD**	21	Cured
10	16	M	Patient DST	Positive	EMB OFX	PZA EMB CPM LFX MFX CYS PAS AMC CLR CFZ **LZD DLM**	20	Cured
11	15	M	Patient DST	Positive	EMB OFX	INH PZA EMB PTO CPM LFX MFX PAS AMC CFZ **LZD**	20	Cured
12	16	M	Patient DST	Positive	EMB OFX	PZA EMB PTO CPM LFX MFX CYS PAS AMC CFZ **LZD DLM** IMI/CIS	20	Cured
13	15	F	Patient DST	Positive	EMB PZA OFX	PZA EMB PTO CPM LFX MFX PAS CFZ **LZD DLM**	12	Not evaluated
14	5	F	Patient DST	Negative	EMB OFX	INH PZA EMB PTO CPM LFX MFX CYS PAS CFZ **LZD**	20	Cured
15	13	F	Patient DST	Positive	EMB PZA	PZA EMB PTO CPM LFX MFX CYS PAS **LZD DLM**	21	Cured
16	14	F	Patient DST	Positive	EMB PZA KM OFX CPM PAS	PZA EMB CPM LFX CYS PAS CFZ **LZD BDQ DLM** IMI/CIN	23	Cured
17	17	M	Patient DST	Positive	EMB PZA	EMB PTO CPM LFX CYS PAS **LZD**	20	Cured
18	16	F	Patient DST	Negative	None	PZA EMB PTO CPM LFX MFX CYS CFZ **DLM**	20	Cured
19	16	M	Patient DST	Positive	EMB PZA	INH PTO CPM LFX MFX CYS PAS CFZ **LZD BDQ**	20	Cured

Abbreviations: AMC, amoxicillin-clavulanate; BDQ, bedaquiline; CFZ, clofazimine; CPM, capreomycin; CYS, cycloserine; DLM, delamanid; DST, drug susceptibility test; EMB, ethambutol; IMI/CIS, imipenem/cilastatin; INH, isoniazid; KM, kanamycin; LFX, levofloxacin; LZD, linezolid; MFX, moxifloxacin; OFX, ofloxacin; PAS, para-aminosalicylic acid; PTO, proteonamide; PZA, pyrazinamide; RIF, rifampicin; STM, streptomycin.
[a]DST results were used to determine treatment regimen (ie, index case DST results were used to determine the treatment regimen for clinically diagnosed patients).

(18.5%), and rash (15.1%). The severity of these AEs was mostly moderate and resolved during the MDR-TB treatment course. Among 4 patients with peripheral neuropathy, 2 had a history of being treated with new and repurposed SLDs and 2 were never treated with new and repurposed SLDs. The 2 patients with peripheral neuropathy ever treated with new and repurposed SLDs received all linezolid, bedaquiline, and delamanid. Similarly, elevated liver enzymes were reported among 2 patients ever treated with new and repurposed SLDs and 2 patients treated with traditional SLDs only. Both patients with elevated liver enzymes ever treated with new and repurposed SLDs group received linezolid (and not bedaquiline nor delamanid). Anemia was rarely seen in our cohort but observed among one pediatric patient treated with linezolid, bedaquiline, and delamanid. Optic neuritis was reported among one pediatric patient during the period where patient was treated with the traditional SLDs (15 days later patient started a new regimen containing linezolid and delamanid). Among 11 pediatric patients treated with delamanid/bedaquiline-containing regimens and received ECG, no patient reported treatment interruption due to QTc prolongation.

DISCUSSION

Our study reported an overall high rate of treatment success among pediatric MDR-TB patients treated in the country of Georgia. The vast majority (>90%) of pediatric patients had newly diagnosed MDR-TB indicating an ongoing transmission of MDR-TB in Georgia. In our cohort, patients receiving treatment regimens that included the new and repurposed SLDs had excellent outcomes. Almost all (94.4%) of the 18 pediatric patients receiving the new and repurposed drugs had favorable treatment outcomes, whereas approximately 80% of patients receiving only traditional SLDs had favorable treatment outcomes. Although nonsignificant, the proportion achieving favorable MDR-TB outcome was modestly higher among patients treated with new and repurposed SLDs compared with patients treated with the traditional SLDs after adjusting for potential confounders. Although we observed a higher risk of experiencing 3 or more AEs among patients treated with the new and repurposed SLDs, the majority of the AEs were not serious and resolved at the end of MDR-TB treatment. Our primary findings suggest that the TB treatment success rate among pediatric patients treated with the new and repurposed SLDs may

Table 3. Crude and Adjusted Cumulative Risk of Favorable Treatment Outcomes Among Pediatric Patients Treated for Multidrug-Resistant Tuberculosis in the Country of Georgia, 2009–2016 (N = 119)

		Treatment Outcomes			
		Favorable[b] N % = 98 (82.3)	Poor[c] N % = 21 (17.7)		
Variables	Total N = 119[a] N %	N %	N %	cRR (95% CI)	aRR (95% CI)
Treatment regimen[d]					
Traditional SLDs	101 (84.9)	81 (80.2)	20 (19.8)	Reference	Reference
New and Repurposed SLDs	18 (15.1)	17 (94.4)	1 (4.8)	**1.18 (1.02-1.37)**	1.17 (0.51-2.72)
Age					
0-5	33 (27.7)	27 (81.8)	6 (18.8)	Reference	Reference
5-10	15 (12.6)	13 (86.7)	2 (13.3)	1.06 (0.82-1.37)	1.16 (0.72-1.88)
11-15	41 (34.5)	36 (87.8)	5 (12.2)	1.07 (0.88-1.31)	1.13 (0.49-2.61)
16-18	30 (25.2)	22 (73.3)	8 (26.7)	0.90 (0.68-1.17)	0.95 (0.10-9.41)
Gender					
Female	45 (37.8)	41 (91.1)	4 (8.9)	Reference	
Male	74 (62.2)	57 (77.0)	17 (23.0)	**0.85 (0.72-0.99)**	
Nationality					
Georgian	107 (90.7)	88 (82.2)	19 (17.8)	Reference	
Other	11 (9.3)	9 (81.8)	2 (18.2)	0.99 (0.74-1.33)	
HIV status					
Negative	60 (48.7)	52 (86.7)	8 (13.3)	Reference	
Positive	1 (0.9)	1 (100.0)	0 (0.0)	1.15 (1.04-1.27)	
Unknown/missing[f]	58 (50.4)	45 (77.6)	13 (22.4)	0.90 (0.76-1.07)	
Case definition					
New	109 (91.6)	92 (84.4)	17 (15.6)	Reference	
Relapse	9 (7.6)	5 (55.6)	4 (44.6)	0.66 (0.37-1.19)	
Retreatment after failure	1 (0.8)	1 (100.0)	0 (0.0)	1.18 (1.09-1.28)	
Baseline sputum smear					
Negative	59 (59.6)	46 (78.0)	13 (22.0)	Reference	
Positive	40 (40.4)	34 (85.0)	6 (15.0)	1.09 (0.90-1.32)	
Missing/not done	20	18	2		
Baseline sputum culture result					
Negative	38 (38.4)	29 (76.3)	9 (23.7)	Reference	Reference
Positive	61 (61.6)	51 (83.6)	10 (16.4)	1.10 (0.89-1.35)	1.06 (0.81-1.39)
Contaminated/missing	20	18	2		
Baseline CXR reading					
Normal	58 (48.7)	46 (79.3)	12 (20.7)	Reference	
Abnormal	61 (52.3)	52 (85.3)	9 (14.8)	1.07 (0.91-1.27)	
Cavitary					
No	112 (94.1)	92 (82.1)	20 (17.9)	Reference	
Yes	7 (5.9	6 (85.7)	1 (14.3)	1.04 (0.76-1.43)	
Infiltration					
No	75 (63.0)	61 (81.3)	14 (18.7)	Reference	
Yes	44 (37.0)	37 (84.1)	7 (15.9)	1.03 (0.87-1.22)	
Fibrosis					
No	95 (79.8)	77 (81.1)	18 (18.9)	Reference	
Yes	24 (20.9)	21 (87.5)	3 (12.5)	1.08 (0.90-1.29)	
TB diagnosis type					
Laboratory confirmed	63(52.9)	52 (82.5)	11 (17.5)	Reference	
Clinical diagnosis[e]	56 (47.1)	46 (82.1)	10 (17.9)	1.00 (0.84-1.18)	
DST availability					
Patients' DST	65 (54.6)	55 (84.6)	10 (15.4)	Reference	
Index Case DST	54 (45.4)	43 (79.6)	11 (20.4)	0.94 (0.79-1.12)	
Drug-resistant type					
RR/MDR TB	69 (59.0)	58 (84.1)	11 (15.9)	Reference	Reference
Pre-XDR/XDR-TB	48 (41.0)	39 (81.3)	9 (18.7)	0.97 (0.82-1.15)	0.91 (0.46-1.81)
Site of disease					
Pulmonary[i]	56 (47.1)	45 (80.4)	11 (19.6)	Reference	Reference
Extrapulmonary	63 (52.9)	53 (84.1)	10 (15.9)	1.05 (0.88-1.24)	1.00 (0.21-4.73)

Table 3. Continued

Variables	Total N = 119[a] N %	Treatment Outcomes: Favorable[b] N % = 98 (82.3) N %	Treatment Outcomes: Poor[c] N % = 21 (17.7) N %	cRR (95% CI)	aRR (95% CI)
TB treatment duration					
Median, month (IQR)	20.2 (18.3-22.6)	20.0 (18.1-20.4)	11.5 (3.9-13.9)		
Sputum conversion at 2 month					
No	91 (76.5)	73 (80.2)	18 (19.8)	Reference	
Yes	28 (23.5)	25 (89.3)	3 (10.7)	1.11 (0.94-1.31)	
Number of hospitalizations					
1	73 (64.0)	59 (80.8)	14 (19.2)	Reference	
>1	41 (36.0)	34 (82.9)	5 (17.1)	1.03 (0.86-1.23)	
Duration of first hospitalization, days					
Median (IQR)	39 (29-65)	42 (31-70)	37 (19-52)		
1-30 days	30 (26.1)	23 (76.7)	7 (23.3)	Reference	
31-60 days	51 (44.4)	42 (82.4)	9 (17.7)	1.07 (0.85-1.36)	
> 60 days	34 (29.6)	30 (88.2)	4 (11.8)	1.15 (0.91-1.45)	
Missing	4	3	1		
Baseline BMI, kg/m^2 (n = 89)					
Median (IQR)	19.0 (17.4-22.0)	19.0 (17.3-21.5)	21.4 (18.1-23.0)		
BMI *z*-score (BMI*z*) classification (n = 80)[g]					
Underweight (BMI*z* < –2.00)	6 (7.5)	5 (83.3)	1 (16.7)	0.93 (0.64 – 1.34)	
Normal (BMI*z* –2.00 to 2.00)	69 (86.3)	49 (89.1)	6 (10.9)	Reference	
Overweight/obese (BMI*z* > 2.00)	5 (6.2)	1 (25.0)	3 (75.0)	0.45 (0.14 – 1.30)	
Missing	39	29	10		
Adverse events					
0	25 (20.0)	19 (76.0)	6 (24.0)	Reference	
1-3	81 (68.1)	67 (82.7)	14 (17.3)	1.09 (0.85-1.39)	
> 3	13 (10.9)	12 (92.3)	1 (7.7)	1.21 (0.93-1.59)	
Adjuvant surgery					
No	100 (87.7)	83 (83.0)	17 (17.0)	Reference	Reference
Yes	14 (12.3)	11 (78.6)	3 (21.4)	0.95 (0.71-1.26)	0.98 (0.38-2.52)
Missing	5	4	1		
Type of surgery					
Segmentectomy	6 (42.9)	5 (45.5)	1 (33.3)		
Lobectomy	5 (35.7)	5 (45.5)	0 (0.0)		
Other[h]	3 (21.4)	1 (9.0)	2 (66.7)		

Bold values indicate that the finding is statistically significant at level of confidence of 5% (2-sided *P*-value <.05).
Abbreviations: aRR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; cRR, crude risk ratio; CXR, chest x-ray; DST, drug susceptibility test; HIV, human immunodeficiency virus; IQR, interquartile range; TB, tuberculosis.
[a]Five patients (2 transferred out and 3 missing) with unknown final MDR-TB treatment outcomes were excluded.
[b]Included patients who were cured or completed treatment according to the WHO guideline.
[c]Included 18 patients who were lost to follow-up, 1 patient for whom treatment was failed, and 2 who died during treatment.
[d]Patients were grouped in "new and repurposed SLDs" category if they received either bedaquiline-, delamanid-, or linezolid during the MDR-TB treatment course.
[e]Among 56 clinically diagnosed pediatric patients, 54 (96%) were treated for MDR-TB based on index case's DST.
[f]In Georgia, HIV testing was not part of the MDR-TB standard care among pediatric patients until 2019.
[g]BMI *z*-score was calculated only among patients aged 2–18 years old.
[h]Included 2 patients who underwent lymphadenectomy and one unknown type of surgery.
[i]Included patients with both pulmonary and extrapulmonary.

be higher when compared with studies conducted among adult patients with MDR-TB (range of success rate among adults was 65%-80% in the previously published studies) [23, 37, 38].

Our findings are consistent with a recent meta-analysis that reported treatment success rates among children treated for MDR-TB were high in both bacteriologically confirmed group (range 60%-100%, pooled treatment success rate 92%, and 95% CI: 0.86-0.96) and clinically diagnosed group (range 75%-100%, pooled treatment success rate 99%, and 95% CI: 0.88-1.00) [39]. However, there have been limited data on the success rate in regard to the use of new and repurposed drugs among pediatric MDR-TB patients. Overall, we found a high proportion of favorable final MDR-TB treatment outcomes among the cohort of pediatric MDR-TB patients (about 80%) and outstanding outcomes among those treated with the new and repurposed SLDs (>90%). This is consistent with findings from a review paper of 8 reports, which reported 85% treatment success rates among 18 children less than 18 years of age treated with linezolid [40].

Table 4. Incidence of Adverse Drug Reactions During Treatment Among Pediatric Patients Treated for Multidrug-Resistant Tuberculosis in the Country of Georgia, 2009–2016 (N = 119)

	Total
Adverse Events	N = 119 N (%)
Any adverse events	**94 (79.0)**
Hypokalemia[a]	14 (11.8)
Nausea	64 (53.9)
Rashes	18 (15.1)
Joint pain (arthralgia)	29 (24.4)
Gastrointestinal tract disturbance	22 (18.5)
Headache	12 (10.1)
Anxiety	22 (18.5)
Optic neuritis	1 (0.8)
Hearing loss	3 (2.5)
Renal failure[b]	1 (0.8)
Peripheral neuropathy	4 (3.4)
Elevated liver enzymes[c]	4 (3.4)
Anemia[d]	1 (0.8)
Itchiness	1 (0.8)
Seizure	5 (4.2)
Thrombocytopenia[e]	2 (1.7)

[a]Hypokalemia was defined when the potassium level (K^+) is less than 3.3 mmol/dL.
[b]Renal failure was defined according to doctor's note in the medical chart.
[c]Elevated liver enzymes were defined if patients had elevated alanine transaminase (ALT) (ie, ALT > 37 U/L) or elevated aspartate transaminase (AST) (ie, AST > 42 U/L).
[d]Anemia was defined by the hemoglobin age-specific cutoff following the Georgian guideline.
[e]Thrombocytopenia was defined when the platelet count is less than 140×10^9/L.

Data regarding the association between the use delamanid and/or bedaquiline and final MDR-TB treatment outcomes among pediatric MDR-TB patients are still scarce. An analysis from the combined trials data reported a dose–response relationship between duration of delamanid prescription and final MDR-TB treatment outcomes (ie, success rate was higher among patients receiving delamanid for ≥6 months [74.5%] vs patients receiving delamanid ≤2 months [55.0%]) [25]. A multinational double-blinded randomized controlled trial conducted among adult patients with MDR-TB reported higher cure rates at 120 weeks among the bedaquiline group (58%) compared with the placebo group (32%) [21]. Unfortunately, we were not able to differentiate the independent effect of delamanid, bedaquiline, or linezolid on the final MDR-TB treatment outcomes among pediatric patients in our cohort due to the relatively small sample size. Moreover, the significant different proportion of pulmonary disease among new and repurposed SLDs groups (39.1%) vs traditional SLDs (84.2%) may affect our observed association. Larger randomized controlled trials will be needed to estimate the efficacy of each of these drugs among pediatric MDR-TB patients.

Although previous studies consistently reported high rates of optic neuropathy, peripheral neuropathy, and anemia among adult patients treated with linezolid [41, 42], the incidence of neuropathy and anemia in our cohort was low. Additionally, the use of bedaquiline and delamanid was associated with an increased risk of QTc prolongation and elevated hepatic transaminase levels in adults [43–45]. However, we did not observe any cases with substantial QTc prolongation among pediatric MDR-TB patients who were treated with bedaquiline- or delamanid-containing regimens in our cohort.

Our study is subject to certain limitations. First, our sample size included only 18 pediatric patients who received the new and repurposed SLDs for the treatment of MDR-TB, substantially fewer compared with those who received a traditional treatment regimen. However, our study is one of the largest pediatric MDR-TB observational study to date with a total sample of 119. Second, nearly half of the pediatric patients included in our cohort were clinical cases and were treated according to their index case's DST. This is not unusual given the difficulty establishing a laboratory-confirmed diagnosis in pediatric patients, especially among children less than 5 years old. This might result in a prolonged duration of MDR-TB treatment, but it is unlikely to affect the final MDR-TB treatment. Third, we did not collect laboratory results or measure clinical factors to systematically define AEs reported in the present paper and this could lead to misclassification. However, as we were working closely with pediatric TB doctors during the data collection and abstraction process, we expected that the proportion of misclassification was low. Furthermore, actions to manage the AEs among our pediatric cohort were not recorded for this research purpose (eg, treatment interruption and dose adjustment). Thus, we were not able to account for regimen change during MDR-TB treatment in our analyses. Additionally, the majority of patients treated with the new and repurposed SLDs were also exposed to traditional SLDs; thus, we were not able to compare the incidence of these AEs between pediatric patients treated with the new and repurposed vs traditional SLDs. Unfortunately, since a substantial proportion of patients in the new and repurposed SLDs group was also exposed to traditional SLDs, we were not able to determine whether AEs observed during the administration of new and repurposed SLDs were not the residual effects of a previous regimen containing traditional SLDs. Furthermore, there may be some degree of cohort effects as we observed different approaches of AE reporting from before 2016 (no pharmacovigilance committee) vs 2016 onwards (pharmacovigilance committee was established). Fourth, a substantial number of pediatric patients in our cohort started the treatment with traditional SLDs and converted their sputum culture to negative before starting the regimen with new and repurposed SLDs. Thus, we were unable to assess the effect of the new and repurposed SLDs on time to achieve sputum culture conversion. Further research including a group of pediatric patients treated with the new and repurposed SLDs at the beginning of MDR-TB initiation and a control/placebo group is needed to better characterize the important role of the new and repurposed SLDs on time to achieve sputum culture conversion (ie, a well-established metric to predict favorable

treatment outcomes) among culture-confirmed pediatric MDR-TB patients.

In conclusion, among a cohort of 119 pediatric patients with MDR-TB in the country of Georgia, the use of the new and repurposed SLDs among pediatric patients with MDR-TB resulted in excellent clinical treatment outcomes. The supply of new and repurposed SLDs in Georgia still relies on international donors and/or collaborators. Thus, the assessment of drug formulation, palatability, and bioavailability may not be feasible as options are limited. Further studies to assess appropriate dose adjustment and pediatric tolerability to the new and repurposed SLDs are still warranted.

Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Supplementary Table 1. Recommended Dosage for Linezolid, Bedaquiline, and Delamanid for Pediatric Patients in the Country of Georgia According to the National Tuberculosis Treatment Guideline, Georgia Ministry of Health, 2019

Supplementary Table 2. Characteristics of Pediatric MDR-TB Patients According to Diagnosis Type, Georgia 2009–2016 (N = 124)

Supplementary Table 3. Distribution of Anti-TB Drugs Prescription Among Patients Receiving Traditional, New, and Repurposed Second-Line TB Drugs in the Country of Georgia, 2009–2016 (N = 124)

Supplementary Table 4. Results From the Sensitivity Analysis With Alternative Definition for "New And Repurposed SLDs" (N = 119)

Notes

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References

1. World Health Organization. Global Tuberculosis Report 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1. Accessed 18 November 2019.
2. World Health Organization. The End TB Strategy. [cited March 29, 2020]. Available at: https://www.who.int/tb/strategy/end-tb/en/. Accessed 29 March 2020.
3. Schaaf HS, Garcia-Prats AJ, McKenna L, Seddon JA. Challenges of using new and repurposed drugs for the treatment of multidrug-resistant tuberculosis in children. Expert Rev Clin Pharmacol **2018**; 11:233–44.
4. Huynh J, Marais BJ. Multidrug-resistant tuberculosis infection and disease in children: a review of new and repurposed drugs. Ther Adv Infect Dis **2019**; 6:1-16.
5. Esposito S, Bosis S, Tadolini M, et al. Efficacy, safety, and tolerability of a 24-month treatment regimen including delamanid in a child with extensively drug-resistant tuberculosis: a case report and review of the literature. Medicine (Baltimore) **2016**; 95:e5347.
6. Harausz EP, Garcia-Prats AJ, Seddon JA, et al. Concise clinical review new and repurposed drugs for pediatric multidrug-resistant tuberculosis practice-based recommendations. **2017** [cited December 6, 2019]. Available at: https://www.tbconsilium.org. Accessed 6 December 2019.
7. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. Lancet Infect Dis **2008**; 8:498–510.
8. Padmapriyadarsini C, Das M, Burugina Nagaraja S, et al. Is chemoprophylaxis for child contacts of drug-resistant TB patients beneficial? A systematic review. Tuberc Res Treat **2018**; 2018:3905890.
9. Zimri K, Hesseling AC, Godfrey-Faussett P, et al. Why do child contacts of multidrug-resistant tuberculosis not come to the assessment clinic? Public Health Action **2012**; 2:71–5.
10. Lee M, Mok J, Kim DK, et al. Delamanid, linezolid, levofloxacin, and pyrazinamide for the treatment of patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis (Treatment Shortening of MDR-TB Using Existing and New Drugs, MDR-END): study protocol for a phase II/III, multicenter, randomized, open-label clinical trial. Trials **2019**; 20:57.
11. Jenkins HE, Yuen CM. The burden of multidrug-resistant tuberculosis in children. Int J Tuberc Lung Dis **2018**; 22:S3–6.
12. Chiang S, Furin J. Treatment of multidrug-resistant tuberculosis in children and adolescents. J Pediatr Infect Dis **2018**; 13:153–68.
13. World Health Organization. Global tuberculosis report 2016. [cited March 29, 2020]. Available at: https://apps.who.int/medicinedocs/en/m/abstract/Js23098en/. Accessed 29 March 2020.
14. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents Interim policy guidance [Internet]. Geneva; **2016** [cited 2020 Mar 29]. Available at: https://www.who.int/tb/publications/Delamanid_interim_policy/en/. Accessed 29 March 2020.
15. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. Eur Respir J **2016**; 48:938–43.
16. Condos R, Hadgiangelis N, Leibert E, et al. Case series report of a linezolid-containing regimen for extensively drug-resistant tuberculosis. Chest **2008**; 134:187–92.
17. Schaaf HS, Willemse M, Donald PR. Long-term linezolid treatment in a young child with extensively drug-resistant tuberculosis. Pediatr Infect Dis J **2009**; 28:748–50.
18. Pinon M, Scolfaro C, Bignamini E, et al. Two pediatric cases of multidrug-resistant tuberculosis treated with linezolid and moxifloxacin. Pediatrics **2010**; 126:e1253–6.
19. Harausz EP, Garcia-Prats AJ, Law S, et al.; Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. Treatment and outcomes in children with multidrug-resistant tuberculosis: a systematic review and individual patient data meta-analysis. PLoS Med **2018**; 15:e1002591.
20. Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies. Infect Dis Poverty **2017**; 6:7.
21. Diacon AH, Lounis N, Dannemann B. Multidrug-resistant tuberculosis and bedaquiline. N Engl J Med **2014**; 371:2436.
22. Pym AS, Cole ST. Mechanism of drug resistance in *Mycobacterium tuberculosis*. In: Wax RG, Lewis K, Salyers AA, Taber H, eds. Bacterial Resistance to Antimicrobials. 2nd ed. Boca Raton: CRC Press; **2007**:313–42.
23. Cox H, Ford N, Hughes J, Goemaere E. Linezolid for multidrug-resistant tuberculosis. Lancet Infect Dis **2013**; 13:16.
24. Sotgiu G, Centis R, D'Ambrosio L, et al. Linezolid to treat extensively drugresistant TB: retrospective data are confirmed by experimental evidence. Eur Respir J **2013**; 42:288–90.
25. Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J **2013**; 41:1393–400.
26. World Health Organization. TB case and treatment outcome definitions – Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children – NCBI Bookshelf. [cited September 3, 2020]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK214446/. Accessed 3 September 2020.
27. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment [Internet]. WHO. Geneva: World Health Organization;

2019 [cited July 13, 2020]. Available at: http://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/. Accessed 13 July 2020.
28. Country Coordinating Mechanism (CCM) Georgia. National strategic plan for tuberculosis control in Georgia 2016–2020 [Internet]. Tbilisi; **2016** [cited March 29, 2020]. Available at: http://tsp.ecom.ngo/files/Tuberculosis-National-Strategic-Plan-2016-2020.pdf. Accessed 29 March 2020.
29. World Health Organization. WHO | Definitions and reporting framework for tuberculosis. **2015** [cited December 19, 2019]. Available at: http://www.who.int/tb/publications/definitions/en/. Accessed 19 December 2019.
30. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? J Am Heart Assoc **2016**; 5:e003264.
31. Division of Microbiology and Infectious Diseases of the National Institutes of Health. Safety reporting and pharmacovigilance | NIH: National Institute of Allergy and Infectious Diseases. [cited September 23, 2020]. Available at: https://www.niaid.nih.gov/research/dmid-safety-reporting-pharmacovigilance. Accessed 23 September 2020.
32. National Cancer Institute of the National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) common terminology criteria for adverse events (CTCAE) v5.0. 2017 [cited September 23, 2020]. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Accessed 23 September 2020.
33. Centers for Disease Control and Preventioon. Growth charts—percentile data files with LMS values. [cited February 24, 2020]. Available at: https://www.cdc.gov/growthcharts/percentile_data_files.htm. Accessed 24 February 2020.
34. Anderson LN, Carsley S, Lebovic G, et al. Misclassification of child body mass index from cut-points defined by rounded percentiles instead of *Z*-scores. BMC Res Notes **2017**; 10:639.
35. De Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? Int J Pediatric Obes **2010**; 5:458–60.
36. Kakkar AK, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. Tuberculosis (Edinb) **2014**; 94:357–62.
37. Mbuagbaw L, Guglielmetti L, Hewison C, et al. Outcomes of bedaquiline treatment in patients with multidrug-resistant tuberculosis. Emerg Infect Dis **2019**; 25:936–43.
38. Kempker RR, Mikiashvili L, Zhao Y, et al. Clinical outcomes among patients with drug-resistant tuberculosis receiving bedaquiline or delamanid containing regimens. Clin Infect Dis **2019**; ciz1107.
39. Harausz EP, Garcia-Prats AJ, Law S, et al.; Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. Treatment and outcomes in children with multidrug-resistant tuberculosis: a systematic review and individual patient data meta-analysis. PLoS Med **2018**; 15:e1002591.
40. Garcia-Prats AJ, Rose PC, Hesseling AC, Schaaf HS. Linezolid for the treatment of drug-resistant tuberculosis in children: a review and recommendations. Tuberculosis **2014**; 94:93–104.
41. Kim CT, Kim TO, Shin HJ, et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. Eur Respir J **2018**; 51:1702467.
42. Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J **2015**; 45:161–70.
43. Cohen K, Maartens G. A safety evaluation of bedaquiline for the treatment of multi-drug resistant tuberculosis. Expert Opin Drug Saf **2019**; 18:875–82.
44. Jones J, Mudaly V, Voget J, et al. Adverse drug reactions in South African patients receiving bedaquiline-containing tuberculosis treatment: an evaluation of spontaneously reported cases. BMC Infect Dis **2019**; 19:544.
45. Ghosh A. Bedaquiline in pediatric drug resistant tuberculosis: is this the next big answer? Clin Infect Dis **2018**, 2:1; e101.