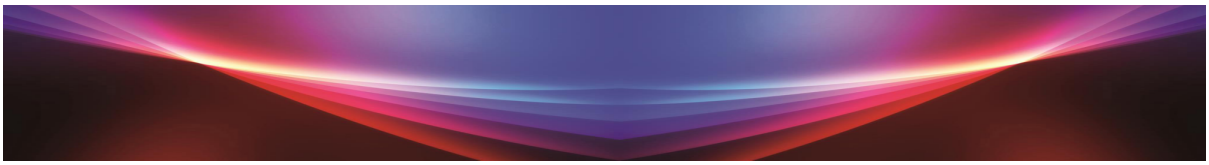

SUPPLEMENTARY MATERIAL

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Effectiveness and safety of delamanid- or bedaquiline-containing regimens among children and adolescents with multidrug resistant or extensively drug resistant tuberculosis: A nationwide study from Belarus, 2015-19

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Supplementary Table 1. Drugs and doses used in treatment of MDR/XDR-TB patients in Belarus, 2015-19.

Drug	**Drug doses by weight group**				
	30-35 kg	**36-45 kg**	**46-55 kg**	**56-70 kg**	**>70 kg**
Moxifloxacin (Mfx)	400 mg	400 mg	400 mg	400 mg	400 mg
Levofloxacin (Lfx)	500 mg	750 mg	1000 mg	1000 mg	1000 mg
Bedaquiline (Bdq)	400 mg for first 2 weeks; then 200 mg od M/W/F				
Linezolid (Lzd)	300 mg	300 mg	600 mg	600 mg	600 mg
Clofazimine (Cfz)	50 mg	100 mg	100 mg	100 mg	100 mg
Cycloserine (Cs) OR Terizidone (Trd)	500 mg	500 mg	500 mg	750 mg	750 mg
Delamanid (Dlm)	200 mg	200 mg	200 mg	200 mg	200 mg
Pyrazinamide (Z)	800 mg	1200 mg	1600 mg	2000 mg	2000 mg
Imipenem/cilastatin (Imp)	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg
Amikacyn (Am)	500 mg	750 mg	750 g	1 g	1 g
Capreomycin (Cm)	500 mg	750 mg	750 mg	1 g	1 g
Prothionamide (Pto) OR Ethionamide (Eto)	500 mg	500 mg	750 mg	750 mg	1000 mg
Amoxicillin/Clavulanic acid (Amx/Clv)	2000 mg/ 500 mg	2000 mg/ 500 mg	2000 mg/ 500 mg	2000 mg/ 500 mg	2000 mg/ 500 mg

Supplementary Table 2. Types of common adverse drug events in MDR/XDR-TB patients treated with bedaquiline and/or delamanid in Belarus, 2015-2019.

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	<LLN - 100 g/L	100-80 g/l	<80 g/L, transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Thrombocytopenia	99.9-75.0x10^9/L	74.9-50.0x10^9/L	49.9-20.0x10^9/L	49.9-20.0x10^9/L	-
Aspartate aminotransferase increased	> ULN - 3.0 x ULN	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	-
Alanine aminotransferase increased	> ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	-
Bilirubin increased	> ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
QTcF prolongation	450 – 480 ms	481-500 ms	>501 ms >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia	-
Hypomagnesaemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Alkaline phosphatase increased	> ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN	-
Blood lactate dehydrogenase increased	ULN - 2.0 x ULN in the absence of acidosis	≥2.0 x ULN in the absence of acidosis	Increased lactate levels at PH <7.3 without life-threatening effects	Increased lactate levels at PH <7.3 in combination with life-threatening effects	-
Creatinine blood increased	1.1-1.5 x ULN	1.6-3.0 x ULN	3.1-6 x ULN	>6 x ULN dialysis required	-
Urea increased	1.25-2.5 x ULN	2.6-5 x ULN	5.1-10 x ULN	>10 x ULN	-
Cardiac disorders	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant but	Life-threatening consequences; urgent	Death

	symptoms; clinical or diagnostic observations only; intervention not indicated	noninvasive intervention indicated; limiting age-appropriate instrumental ADL	not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	intervention indicated	
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

ADL, activities of daily living; LLN, lower limit of normal; ULN, upper limit of normal; QTcF, adjusted QT interval using Fredericia formula.

Supplementary Table 3. Management, outcomes and timing of adverse drug events in children and adolescents with multi/extensively drug-resistant tuberculosis who received bedaquiline or delamanid, 2015-2019, Belarus (N=40).

	Total number of AE	AE management				Proportion of AE with resolved outcome, n (%)°	Time to AE			Duration of AE*		
		Drug withdrawn	Drug interruption	Dose reduction	Dose maintained		Median time to AE [25th-75th percentiles]	Earliest onset, days	Latest onset, days	Median duration of AE [25th-75th percentiles]	Minimum duration, days	Maximum duration, days
Eosinophilia	23	–	–	–	23	23 (100)	67 [51-133]	22	628	91 [34-103]	12	376
Anaemia	22	–	2	5	15	22 (100)	76 [44-122]	23	488	102 [50-211]	29	490
AST increased	18	–	1	–	17	18 (100)	311 [89-434]	27	629	95 [63-236]	23	517
Cardiac disorders	17	–	–	–	17	13 (76.5)	63 [30-147]	22	461	124 [84-204]	31	573
Corrected QT interval prolongation	17	–	–	–	17	17 (100)	86 [59-113]	25	340	57 [22-99]	3	217
Creatinine increased	15	–	–	–	15	14 (93)	32 [25-111]	8	345	183 [57-218]	20	256
ALT increased	10	–	1	–	9	9 (90)	116 [84-277]	27	629	103 [51-324]	11	530
Hypocalcaemia	10	–	–	–	10	7 (70)	276 [193-358]	153	492	74 [33-272]	10	499
Thrombocytopenia	10	–	–	4	6	10 (100)	101 [29-231]	20	582	44 [24-68]	10	518
AP increased	7	–	–	–	7	5 (71)	342 [93-408]	50	637	91 [84-395]	62	398
Bilirubin increased	6	–	–	–	6	6 (100)	87 [69-144]	60	203	138 [72-195]	30	329
Hyperuricemia	5	–	–	–	5	5 (100)	83 [69-133]	29	461	125 [125-344]	31	645
Hypomagnesaemia	5	–	–	–	5	5 (100)	73 [31-84]	2	203	102 [65-161]	52	525
LDG increased	5	–	–	–	5	4 (80)	342 [280-418]	151	438	122 [84-190]	21	326
Leukopenia	5	–	–	2	3	5 (100)	60 [56-96]	29	126	65 [31-84]	23	610
Joint pain	4	–	–	–	4	4 (100)	47 [13-207]	11	336	35 [18-98]	7	153
Headache	3	–	–	–	3	3 (100)	57 [9-64]	9	64	5 [2-18]	2	18
Urea increased	3	–	–	–	3	3 (100)	112 [31-443]	31	443	90 [20-271]	20	271
Other	39	1[a]	1	3	34	37 (95)	127 [46-274]	2	532	32 [11-84]	0	367
Total	224	1	5	14	202	210 (94)	91 [50-240]	2	637	84 [31-181]	0	645

AE, adverse events; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; °polyneuropathy of lower limbs due to linezolid; *if AE was not resolved, duration is the difference between AE onset date and date of final treatment outcome.

Supplementary Table 4. Incidence rate of adverse drug events by organ systems in children and adolescents with multi/extensively drug-resistant tuberculosis who received bedaquiline or delamanid, 2015-2019, Belarus (N=40).

	Total number of AE, n	Incidence rate per 100 person-months [95% CI]
Blood and lymphatic system disorders	62	8.0 [6.1-10.2]
Cardiovascular disorders and investigations	43	5.5 [4.0-7.4]
Eye disorders	2	0.3 [0.0-0.9]
Gastrointestinal disorders and investigations	6	0.8 [0.3-1.7]
Hepatobiliary disorders and investigations	34	4.3 [3.0-6.1]
Investigations	13	1.7 [0.9-2.8]
Metabolism and nutrition disorders	26	3.3 [2.2-4.9]
Musculoskeletal and connective tissue disorders	4	0.5 [0.1-1.3]
Nervous system disorders	6	0.8 [0.3-1.7]
Psychiatric disorders	2	0.3 [0.0-0.9]
Renal and urinary disorders and investigations	18	2.3 [1.4-3.6]
Respiratory, thoracic and mediastinal disorders	2	0.3 [0.0-0.9]
Skin and subcutaneous tissue disorders	5	0.6 [0.2-1.5]
Sleep disorders	1	0.1 [0.0-0.7]
Total	224	28.6 [25.0-32.6]

Supplementary Table 5. Cumulative incidence rate of adverse drug events along the follow up in children and adolescents with multi/extensively drug-resistant tuberculosis who received bedaquiline or delamanid, 2015-2019, Belarus (N=40).

Time period	Incidence rate	95% confidence interval lower limit	95% confidence interval upper limit
[0;1)	92.5	65.1	127.5
[1;2)	91.3	71.5	114.7
[2;3)	94.2	77.6	113.2
[3;4)	82.5	69.0	97.8
[4;5)	74.0	62.6	86.9
[5;6)	64.9	55.0	75.9
[6;7)	57.9	49.3	67.6
[7;8)	53.2	45.4	61.8
[8;9)	48.3	41.3	56.1
[9;10)	46.7	40.1	54.0
[10;11)	43.1	37.0	49.8
[11;12)	42.2	36.4	48.5
[12;13)	40.0	34.6	46.0
[13;14)	38.2	33.1	43.8
[14;15)	37.5	32.6	42.9
[15;16)	36.2	31.5	41.3
[16;17)	34.5	30.1	39.5
[17;18)	33.0	28.8	37.7
[18;19)	32.0	27.9	36.5
[19;20)	31.5	27.5	35.9
[20;21)	30.6	26.8	34.9
[21;22)	30.0	26.2	34.2
[22;23)	29.5	25.7	33.6
[23;24)	29.3	25.6	33.4
[24;25)	28.6	25.0	32.6