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Multidrug-resistant tuberculosis in children in Northwest Russia: an observational cohort study

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'Take home' message: High proportion of children with MDR-TB had favourable outcome (90%) with early diagnosis and treatment initiation.

Multidrug-resistant tuberculosis in children in Northwest Russia: an observational cohort study

Russia has the third highest absolute number of multidrug-resistant (MDR) tuberculosis (TB) cases in the world [1], yet little is known about the scale of childhood MDR-TB in the country; available publications are limited to small case series in older children [2,3]. Successful treatment outcomes for children with MDR-TB vary widely in other settings, ranging from 53% to 97% [4].

The Arkhangelsk Region has one of the highest rates of MDR-TB in Russia [5]. The first paediatric MDR-TB case was registered in 2001. The Arkhangelsk Regional Tuberculosis Dispensary, a State Healthcare tertiary TB centre, coordinates care for all patients with drug-resistant TB in the region and works closely with two paediatric sanatoriums.

We conducted a retrospective cohort study of all children (<18 years) diagnosed with MDR-TB in the region, from 01/01/2001 to 31/12/2012 with follow-up data to 31/12/2015. Data were extracted from patient health records and treatment cards. In the Russian national TB programme, childhood TB is disaggregated into younger children (<15 years) and adolescents (15 to <18 years). This cut-off was preserved to align with country reporting.

MDR-TB was considered as confirmed or clinically-diagnosed. Confirmed cases were verified by culture and drug sensitivity testing and/or molecular testing. Clinically-diagnosed cases were defined according to published consensus definitions [6] and TB severity was categorised based on established criteria [7]. Children with sputum smear- or culture-positive MDR-TB were treated as in-patients at the Dispensary until they were considered non-infectious; most sputum culture-negative cases were treated in the paediatric sanatoriums. A few children were managed at home with directly observed therapy (DOT).

Tuberculin skin testing (TST) was performed at baseline and repeated at six weeks if initially negative. Toxicity monitoring included full blood count, blood biochemistry, urinalysis, thyroid stimulating hormone (TSH) and hearing evaluation. Children ≥4 years treated in the Dispensary underwent pure tone audiometry; all children <4 years and children treated in sanatoriums had whispered voice testing administered by trained clinicians. Patients treated with ethambutol underwent monthly ophthalmology review. Other paediatric specialists (endocrinologists, nephrologists and psychologists) reviewed children as required.

Treatment outcomes were classified as per WHO definitions [8]. Comparisons between baseline characteristics in the two age groups were made using Fisher's exact test for categorical variables and Wilcoxon's rank-sum (Mann-Whitney) test for continuous variables, and unadjusted Poisson regression was used to compare the number of grade 3-4 events. Statistical analyses were done with Stata version

14.0. Written informed consent was obtained from children's families at the time of MDR-TB diagnosis. The study received research ethics approval from the Northern State Medical University, Arkhangelsk.

Over the study period, the TB incidence rate in children decreased from 12-15 per 100,000 population in 2001-2009 to 7-9/100,000 in 2010-2012; the proportion of MDR cases ranged from 4.9 to 42%. Overall, of 366 children diagnosed with TB, 56 (15%) were MDR. Clinical and treatment characteristics were available for 52 children. Median age at diagnosis was 10.6 years (interquartile range (IQR): 5.0-15.9). Overall, in 48 (92%) children an adult source case with MDR-TB was identified; 33 (63%) children were diagnosed following contact screening. Twenty-eight (54%) children were asymptomatic and 41 (79%) had TST induration ≥10mm. Twenty-eight (54%) children had pulmonary TB; seven had cavities. All children were tested for HIV; none were positive. Seventeen children (33%) had confirmed MDR-TB: 16 had positive culture, including one child with XDR-TB, and 1 was confirmed by nucleic acid amplification test (GenoTypeMTBDRplus) only. Nine (17%) had severe TB at diagnosis (Table).

Most children were treated in hospital or sanatoriums; only three had full treatment at home. Overall median treatment duration was 21.7 months (IQR 17.0-24.0). Treatment regimens were constructed based on the existing WHO recommendations. Younger children received a shorter duration of injectable drugs compared to adolescents ($p<0.001$) (Table).

Adverse reactions were experienced by 25 (48%) children. Eight children had 10 moderate to severe reactions (5 raised transaminases, 5 eosinophilia), with temporary treatment interruption in four (3 drug-induced hepatitis, 1 severe eosinophilia). One child had treatment discontinuation due to mild renal toxicity. Nausea and/or vomiting were observed in 5 of 40 (13%) children treated with prothionamide. Twenty children (38%) developed increased liver transaminases. TSH elevation was observed in 15 children treated with prothionamide and/or PAS (15/48, 31%); all remained asymptomatic and received levothyroxine until MDR-TB treatment completion. Two children on cycloserine (2/41, 5%) had emotional liability and irritability. Four children (4/52, 8%) complained of persistent knee joint pain; one had elevated uric acid and received allopurinol. One of 26 children tested by pure tone audiometry had mild hearing loss. All other children were tested by whispered voice; they had no clinically significant hearing loss during follow-up.

All 52 children were followed up for at least 18 months post treatment; none were lost to follow-up. Forty-seven (90%) had successful outcomes (16 achieved cure and 31 completed treatment). Three children did not complete treatment: one stopped after 3.7 months for drug-related nephrotoxicity and two adolescents discontinued at 7.7 and 12.4 months. All three were sputum smear/culture-negative and improved despite premature treatment discontinuation. One child relapsed; completed a 14 months re-treatment regimen without recurrence. One patient, diagnosed aged 13 years with sputum

smear/culture-positive MDR-TB, resistant to all first-line drugs and ethionamide, died at age 21 years from extensive pulmonary TB.

Most children (63%) were identified through contact screening. In contrast to other contexts with high rates of TB in children aged less than five years [9], our data show a relatively low proportion of the caseload in this age group. This is consistent with another study from Pakistan which demonstrated that children aged over five years had similar rates of MDR-TB to younger children [10]. Over half of the children were asymptomatic with only radiological manifestations at diagnosis, and two-thirds had clinically-diagnosed MDR-TB. The findings suggest that contact tracing and subsequent close follow-up allowed early diagnosis of MDR-TB; the decision to treat children with symptoms suggestive of TB and contact history without bacteriological confirmation allowed for timely treatment initiation.

Successful outcomes were achieved in 90% of children. Younger children had predominantly non-severe TB and a shorter duration of injectable treatment. This is consistent with other paediatric studies [4, 11, 12]. Our study showed high rates of successful treatment in adolescents in contrast to other recent studies reporting poor outcomes in this age group [13,14]. Daily DOT administered by medical personnel may well have contributed to this. Although nearly half of the children experienced adverse reactions, most were actively managed, allowing continuation of the prescribed regimen in most children.

This study has limitations of retrospective design and suboptimal hearing assessment in most children, therefore, the hearing loss was likely to be underestimated.

The treatment of MDR-TB in children is complex, challenging, of long duration, and is associated with high rates of adverse reactions. Improved regimens are urgently needed and the new drugs, bedaquiline and delamanid, could play a more prominent role in paediatric MDR-TB treatment [15,16]. In spite of this, however treatment success was achieved in most children with a proactive approach to contact tracing, early treatment based on clinical diagnosis, structured approach to the construction of drug regimens based on the international recommendations, and the active management of adverse reactions.

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Table 1 Multidrug-resistant tuberculosis in children in the Arkhangelsk region: baseline characteristics at diagnosis, treatment duration and outcome.

	Children (<15 years at diagnosis) (n=36)	**Adolescents (15 to <18 years at diagnosis) (n=16)**	**Overall (n=52)**	**P-value**
	median (IQR) or n (%) or number of events (number of patients)			
Age at diagnosis of MDR-TB disease	7.0 (4.1, 10.9)	16.6 (15.9, 17.2)	10.6 (5.0, 15.9)	n/a
Male gender	13 (36%)	8 (50%)	21 (40%)	0.3753
Methods of case finding				0.2203
Contact tracing	25 (69%)	8 (50%)	33 (63%)	
Annual routine TST screening¤	6 (17%)	3 (19%)	9 (17%)	
Fluorography screening¤	-	3 (19%)	3 (4%)	
Presented with symptoms	5 (14%)	2 (13%)	7 (13%)	
Identified source case with MDR-TB	32 (89%)	16 (100%)	48 (92%)	0.2988
TST				0.2377
<5mm	5 (14%)	0	5 (10%)	
5-<10mm	3 (8%)	3 (18%)	6 (12%)	
≥10mm	28 (78%)	13 (81%)	41 (79%)	
Type of MDR-TB				0.0001*
Pulmonary only	5 (14%)	12 (75%)	17 (33%)	
Extrapulmonary only	21 (58%)	3 (19%)	24 (46%)	
Pulmonary and extrapulmonary	10 (28%)	1 (6%)	11 (21%)	
Presenting symptoms				0.0384
TB-related symptoms§	13 (36%)	11 (69%)	24 (46%)	
Asymptomatic	23 (64%)	5 (31%)	28 (54%)	
Microbiological confirmation				0.3400
Positive culture or NAAT	10 (28%)	7 (44%)	17 (33%)	
Severity of disease				0.1132
Severe	4 (11%)	5 (31%)	9 (17%)	
Non-severe	32 (89%)	11(69%)	43 (83%)	
Treatment duration				
Duration of hospital admission in months (n=5,10,15)	3.0 (2.7, 6.3)	4.5 (3.0, 5.5)	4.1 (3.0, 5.7)	0.8065
Duration of sanatorium treatment in months (n=31,5,36)	18.1 (14.9, 22.6)	8.2 (6.7, 12.3)	17.6 (12.6, 22.1)	0.0163
Duration of treatment in months	20.8 (16.4, 22.8)	22.8 (19.2, 26.4)	21.7 (17.0, 24.0)	0.1268
Duration of treatment with injectables in months (n=33,16,49)‡	4.3 (3.0, 6.1)	7.6 (6.2, 9.3)	5.9 (3.3, 7.4)	0.0002
Grade 3-4 adverse reactions¥	6 (5)	4 (3)	10 (8)	0.5299#
Elevated ALT and/or AST	4	1	5	
Eosinophilia (asymptomatic)	2	3	5	
Outcome				0.6374^
Favourable outcome	33 (92%)	14 (88%)	47 (90%)	
Cure	9	7	16	
Treatment completed	24	7	31	
Unfavourable outcome	3 (8%)	2 (13%)	5 (10%)	
Relapse or recurrence of MDR-TB	1	0	1	
Treatment incomplete	1	2	3	
Treatment failed, died	1	0	1	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; LN: lymph nodes; NAAT: nucleic acid amplification tests; n/a: not applicable; TST: tuberculin skin test. ¤ Part of routine TB screening in Russia: annual TST in all children and two yearly fluorography in children aged 15-18 years. § Cough, fever, weight loss of any duration. ǂ Three children were not treated with injectables: two had TB nephritis, and the third had disease caused by M. tuberculosis resistant to both capreomycin and kanamycin.*Comparison between pulmonary only TB and other forms. ¥ Grading of the adverse reactions adapted from Division of Microbiology and Infectious Diseases (DMID) paediatric toxicity tables, 2007. #Comparison of number of events. ^ Comparison between favourable and unfavourable outcomes.