EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Short oral treatment regimens for rifampicin-resistant tuberculosis are safe and effective for young children: results from a field-based non-randomized clinical trial, Kandahar Afghanistan

Anita Mesic, Ine Decuyper, Sadiqqullah Ishaq, Taiba Azizi, Fazal Hadi Ziamal, Shirbaz Amiri, Kees Keus, Moe Thandar Pyae, Khan Mohammed Mangal, Hashim Khan Amirzada, Assadullah Rasooli, Mohammad Reza Aloudal, Mohammad Zaher Daldar, Tom Decroo

Please cite this article as: Mesic A, Decuyper I, Ishaq S, *et al*. Short oral treatment regimens for rifampicin-resistant tuberculosis are safe and effective for young children: results from a field-based non-randomized clinical trial, Kandahar Afghanistan. *Eur Respir J* 2024; in press (https://doi.org/10.1183/13993003.00436-2024).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Short oral treatment regimens for rifampicin-resistant tuberculosis are safe and effective for young children: results from a field-based non-randomized clinical trial, Kandahar Afghanistan

Anita Mesic[1,2*], Ine Decuyper[2], Sadiqqullah Ishaq[3], Taiba Azizi[3], Fazal Hadi Ziamal[4], Shirbaz Amiri[3], Kees Keus[1], Moe Thandar Pyae[3], Khan Mohammed Mangal[5], Hashim Khan Amirzada[5], Assadullah Rasooli[5], Mohammad Reza Aloudal[6], Mohammad Zaher Daldar[5], Tom Decroo[2]

[1]Médecins Sans Frontières, Public Health Department, Plantage Middenlaan 14, 1018 DD Amsterdam, The Netherlands

[2]Institute of Tropical Medicine, Department of Clinical Sciences, Kronenburgstraat 43, 2000 Antwerp, Belgium

[3]Médecins Sans Frontières, District 2, Kandahar, Islamic Republic of Afghanistan

[4]Médecins Sans Frontières, Qual-e-Fathullah, Street 2, Kabul, Islamic Republic of Afghanistan

[5] Ministry of Public Health, National Tuberculosis Program, Darul Aman, District 6, Kabul, Islamic Republic of Afghanistan

[6]World Health Organisation, Jalalabad Road, Pul-e-Charkhi, Kabul, Islamic Republic of Afghanistan

*Corresponding author

Email: anitamesic@gmail.com

To the Editor,

Clinical trials, evaluating 9-month/7-drug and 6-month/4-drug all-oral rifampicin-resistant tuberculosis (RR-TB) treatment regimens showed that these are at least as effective and safer than previously used longer and injectable-containing regimens [1-4]. Findings directly informed World Health Organization (WHO) guidelines for the treatment of adults with RR-TB, including pre-extensively drug-resistant TB (pre-XDR-TB; RR-TB with resistance to fluoroquinolones, FQ) [5]. However, children were not included in these trials. Especially for children with pre-XDR-TB, severe TB disease, or extrapulmonary TB (other than peripheral lymphadenitis) this has dire consequences. They are still treated with individualized 18-month regimens, which are not only longer, but also more toxic, less effective and with a higher pill burden than regimens for adults with a similar condition [5, 6].

In the context of Afghanistan, most TB cases occur among women and children, with an estimated 15,000 new paediatric TB cases every year [8]. Although the estimated number of children with incident RR-TB in the country is unknown, we have observed a high burden of paediatric RR-TB among close household contacts of adult patients with confirmed RR-TB disease in Afghanistan [9]. Therefore, it was essential to evaluate the effectiveness and safety of shorter RR-TB regimens in children in this context. In 2019, Médecins sans Frontières (MSF), in collaboration with the National Tuberculosis Control Programme, implemented a cohort study to assess effectiveness and safety of 9-month short oral regimens in Kandahar, Afghanistan, from November 2019 until April 2023. Children 14 years and younger were enrolled, if they were diagnosed with RR-TB disease, based on microbiological confirmation or household contact history combined with clinical and radiographic signs. Four study regimens were designed based on the 2018 WHO recommendations, accounting for the participants' age and baseline FQ resistance [10]. In case of known pre-XDR-TB, and if 6 years or older, levofloxacin was replaced by delamanid. Cycloserine was used in children under the age of 6 years with pre-XDR-TB. Treatment was delivered at home as family-based directly observed treatment unless children required hospitalization. Treatment success was defined as a cure or treatment completion, after minimum of 36 weeks of treatment and if microbiological and clinical examination and chest radiography showed that signs of

tuberculosis disease had resolved. Unfavourable outcomes were death, lost-to follow-up, and treatment failure, defined in the WHO guidelines [5]. The final favourable outcome was relapse-free treatment success, assessed at 18 months after treatment completion.

Median age among 27 participants was 3.8 (Interquartile range, IQR 1.9-6.5) years. Twenty-two (81%) were identified through active case finding among household contacts of known RR-TB cases. Microbiological confirmation was achieved in 19 (70%) participants, either on Xpert MTB/RIF (18/19) and/or culture (3/19). Eight (30%) participants were diagnosed clinically among close contacts of patients with RR-TB. Pulmonary tuberculosis (PTB) was identified in 24 (89%) participants. Three (11%) children had extrapulmonary TB (EPTB), with locations in the spine, abdomen and cervical lymph nodes. The mean Weight-for-Age Z (WAZ) score at baseline was -1.80 (Standard Deviation, SD 2.53). For 19/27 (70%) participants the baseline FQ susceptibility status was available, either by testing direct participant's sample or using the result of the presumed index case as a proxy. Eight participants (of 27, 42%) had pre-XDR-TB. In six (75% of 8 with pre-XDR) FQ resistance was known before treatment started, while two (25%) received test result after treatment completion. In 20/27 (74%) of participants, severe TB disease was diagnosed, based on WHO criteria [6]. Median treatment duration was 275 (IQR 274-295) days. We observed 86 episodes of adverse events among 23 children, including two severe adverse events (anemia and electrolyte disbalance), defined by the endTB Clinical Trial Clinical Guidelines [7]. Twenty-four (89%) participants were cured (n=3) or completed treatment (n=21). The mean WAZ score at the end of the treatment was – 0.64 (SD 1.85). WAZ score difference between baseline and end of treatment result was 1.15 (SD 2.11; p=0.01). Two (7%) children died. One death was related to hematological malignancy, for which no treatment was available. The second patient died due to clinically diagnosed secondary bacterial peritonitis. One participant, treated for abdominal EPTB, was declared to have treatment failure, due to lack of clinical response. None of the participants was lost to follow-up during treatment. Among 24 participants who successfully completed their treatment, 23 (96%) were without clinical, radiological or microbiological proof of TB disease recurrence at 18 months post-treatment. One participant was lost to follow-up at 6 months post-treatment but did not show any signs or symptoms of disease recurrence at the last visit.

Results of our study demonstrated that 9-month regimens for RR-TB disease were safe and effective in 27 children, with a median age of 3.8 years in Kandahar, Afghanistan. Despite the majority having severe TB disease, 85.2% achieved recurrence-free treatment success, measured at 18 months after treatment completion. Observed adverse events were rarely severe and did not cause treatment interruption or treatment change. Because microbiological confirmation of TB disease is possible only in approximately 30% of paediatric cases [11], treatment outcomes in young children are often assessed by clinical and radiological signs of disease resolution. In this study, only one participant showed treatment failure, based on poor clinical resolution of abdominal RR-TB lesions. Shortening of treatment duration increases the risk of relapse, which more frequently occurs within the first six months post-treatment [12]. Eighteen months after treatment completion, and with data available for 23 of 24 children, none of our participants was reported having clinical, radiographic, or microbiological signs of RR-TB disease recurrence, confirming the effectiveness of the regimens used. In adults enrolled in the endTB clinical trial, the same short regimens were non-inferior to standard of care [13]. For children not eligible for the highly effective 6-month pretomanid-containing regimens, alternative evidence-based treatment options are needed. Short 9-month RR-TB treatment is not recommended in children with pre-XDR-TB. However, in our study, patients with pre-XDR, were treated with 9-month regimens (8/8, 100%). Two patients with FQ resistance (known after treatment was completed) were successfully treated with FQ-containing regimens, relying on the effectiveness of other drugs in the regimen. Another eight patients with unknown FQ susceptibility status were treated successfully with studied regimens. Our findings are consistent with previous reports showing that short regimens containing newer and repurposed drugs may also be safe and effective in children with complex patterns of drug resistance [14-16]. In children with microbiologically confirmed RR-TB, and eligible for shortened treatment, drug susceptibility testing results will be needed for the main drugs used in the regimen [17]. Unfortunately, drug susceptibility testing for bedaquiline, linezolid, and delamanid is not yet available in most high burden countries.

Children with RR-TB are one of the most vulnerable, yet the most neglected population with TB. Despite their better response to RR-TB treatment, current practice in most of the settings is to treat children with longer and more toxic regimens than adults. While waiting for high-quality scientific evidence we should not continue with this unacceptable practice. Results of the endTB clinical trial, combined with our results provide sufficient evidence that pragmatic alternatives are available and can result in improved quality of care in children treated for RR-TB [11].

This is the first report from a field-based observational study on the use of short oral regimens in a very young population affected by RR-TB. High data quality allowed for a detailed analysis of safety and response to treatment. Post-treatment follow-up time was longer than reported in previous clinical trials, showing recurrence-free treatment success. However, there was no randomization, including to a standard of care control group. The sample size was small, limiting the precision of any estimate of the treatment effect. In that regard it is reassuring that the observed results are consistent with the results from the endTB randomized clinical trial [11]. The generalizability of our results is limited. To confirm our findings, operational research during the implementation of the regimens presented here is needed in paediatric populations in various contexts, closely monitoring safety and effectiveness data.

Furthermore, it is also possible that for many children these regimens still contained too many pills and that treatment duration can be shortened further. High level of recurrence-free treatment success justifies future research on further shortening of RR-TB treatment regimen duration in this population, especially in those with less severe disease.

Table 1: Baseline demographic and clinical characteristics, treatment regimens and final treatment outcomes for rifampicin-resistant tuberculosis among the participating children (n=27)

Regimen	Total children on regimen	Gender		Positive contact history	Severe CXR findings	Microbiological Confirmation[1]	Severe TB disease[2]	Baseline fluoroquinolone susceptibility[3]			Recurrence-free success 18 months post-treatment
		Male	Female					S	R	UK	
	N (%)	N	N	N	N	N	N	N	N	N	N
Bdq, Lfx, Lzd, Cfz, Z[2]	7 (26.0)	3	4	6	4	5	7	3	2[4]	2	7
Bdq, Dlm, Lzd, Cfz, Z	3 (11.0)	2	1	1	1	2	2	0	0	3	2[5]
Lfx, Dlm, Lzd, Cfz, Z	9 (33.0)	5	4	7	4	6	8	7	0	2	7[6]
Dlm, Lzd, Cfz, Cs, Z	8 (30.0)	5	3	8	2	6	3	1[7]	6	1	7[8]
Total N (%)	27 (100.0)	15 (55.6)	12 (44.4)	22 (81.5)	11 (40.7)	19 (70.3)	20 (74.0)[9]	11 (40.8)	8 (29.6)	8 (29.6)	23 (85.2)

Legend: CXR – chest radiography; S-susceptible; R- resistant; UK- unknown; Bdq – bedaquiline; Lfx – levofloxacin; Lzd – linezolid; Cfz – clofazimine; Z – pyrazinamide; Dlm – delamanid; Cs – cycloserine;

[1] Microbiological confirmation of tuberculosis disease based either on positive culture or Xpert MTB/RIF test result at baseline.

[2] Pyrazinamide resistance testing was performed only in a subgroup of patients with a positive culture test result (n=3), resulting in all susceptible results. Pyrazinamide resistance was detected among 27% (6/22) of the tested index cases.

[3]Severe tuberculosis disease is defined by the WHO as presenting with any of the following: presence of respiratory, neurological and/or gastrointestinal danger signs and/or with asymmetric and persistent wheezing, and/or EPTB other than lymph node disease and/or severe acute malnutrition, and/or respiratory distress and/or fever > 39.0 C and/or severe pallor and/or lethargy and/or restlessness and/or severe chest radiography findings, and/or bacteriologically confirmed TB (other than low or very low at the Xpert MTB/RIF result or trace call at Xpert Ultra result).

[4] Established either by phenotypic or genotypic drug susceptibility test result of the participant and/or index case (an adult close household contact).

[5] Susceptibility test result known after treatment completion.

[6] One participant with unknown baseline fluoroquinolone-susceptibility failed treatment regimen.

[7]One participant with unknown and one with confirmed baseline fluoroquinolone-susceptibility died before the end of the treatment.

[8] One participant was lost to follow-up at six months weeks post-treatment.

[9] Out of total n=27

Footnotes

STROBE statement: The paper followed the standards for reporting observational studies outlined in the Strengthening the Reporting of Observational studies in Epidemiology, available here: https://strobe-statement.org/index.php?id=strobe-home.

Ethics: The study was approved by the Institutional Review Board (IRB) of the Ministry of Public Health, Afghanistan (A08190063); the IRB of the Institute of Tropical Medicine, Antwerp (1329/19); the Ethical Review Board of the University of Antwerp (19/49/566); and the MSF independent Ethical Review Board (ERB; 1933/19). Informed consent was signed by the legal guardian for all participants. An independent data and safety monitoring committee reviewed safety and effectiveness data throughout the trial.

Conflicts of interest: The authors have no potential conflicts of interest to disclose.

Dr Mohammad Reza is the employer of WHO regional office, Kabul, Afghanistan. The findings and conclusions in this article are those of the author and do not necessarily represent the views of the World Health Organization.

Support statement: Supported by Médecins Sans Frontières. Following authors received salary from Médecins Sans Frontières during the study period: AM, SI, TA, FHZ, SA, KK and MTP.

Authors' contributions: AM, ID and TD conceptualised and designed the study. AM and SI, TA, FHZ, SA, KMM, AR, MRA and MZD contributed to study implementation. AM was responsible for the data analysis. All authors participated in the data interpretation. AM drafted the original manuscript. All authors had major contributions to manuscript writing and all approved the final version of the manuscript.

Acknowledgements: We would like to acknowledge the contribution of the study participants, laboratory, medical, and data teams.

References

1. Nyang'wa B-T, Berry C, Kazounis E, *et al*. A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2022;387(25):2331-43.
2. Conradie F, Diacon AH, Ngubane N, *et al*. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. N Engl J Med. 2020;382(10):893-902.
3. Conradie F, Bagdasaryan TR, Borisov S, *et al*. Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med. 2022;387(9):810-23.
4. Nunn AJ, Phillips PPJ, Meredith SK, *et al.* A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2019;380(13):1201-13.
5. World Health Organization. Rapid Communication: Key Changes to the Treatment of Drug-resistant Tuberculosis. Geneva, World Health Organization, 2022. Report number: WHO/UCN/TB/2022.2.
6. endTB Consortium. endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Paris, endTB Consortium, 2018. Version 4.0.
7. WHO operational handbook on tuberculosis Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Ogranisation; 2022.
8. World Health Organization. Global Tuberculosis Report 2022. Geneva, World Health Organization, 2022.
9. Mesic A, Ishaq S, Khan WH, *et al*. Person-centred care and short oral treatment for rifampicin-resistant tuberculosis improve retention in care in Kandahar, Afghanistan. Trop Med Int Health. 2022;27(2):207-15.
10. World Health Organization. Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampicin-resistant Tuberculosis (MDR/RR-TB). Geneva, World Health Organization, 2018. Report number: WHO/CDS/TB/2018.18.
11. Marais BJ, Hesseling AC, Gie RP, *et al*. The Bacteriologic Yield in Children with Intrathoracic Tuberculosis. Clin Infect Dis. 2006;42(8):e69-e71.
12. Luzze H, Johnson DF, Dickman K, *et al*. Relapse more common than reinfection in recurrent tuberculosis 1-2 years post treatment in urban Uganda. Int J Tuberc Lung Dis. 2013;17(3):361-7.
13. Efficacy results in a study of five all-oral, shortened regimens for MDR/RR-TB [abstract]. In: Innovation to guide practice in MDR/RR-TB treatment: efficacy and safety results of the endTB trial. 53rd World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union): November 15 – 18 2023; Paris. https://theunion.org/our-work/conferences/history-of-the-union-world-conference-on-lung-health/conference-abstract-books. Date last accessed 12 March 2024.
14. Sun WW, Yang M, Chen XH, *et al.* Efficacy and safety of the all-oral bedaquiline-containing regimen as treatment for pediatric multidrug/rifampicin-resistant tuberculosis: a multicenter, retrospective, cohort study. Expert Rev Anti Infect Ther. 2023:1-9.
15. Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, Delamanid, Linezolid and Clofazimine for Treatment of Pre-extensively Drug-Resistant Tuberculosis. Clin Infect Dis. 2022;76(3):e938-46.
16. Pecora F, Dal Canto G, Veronese P, *et al.*Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Children: The Role of Bedaquiline and Delamanid. Microorganisms. 2021;9(5).
17. Achar J, Seddon JA, Knight GM, *et al*. Guiding pragmatic treatment choices for rifampicin-resistant tuberculosis in the absence of second-line drug susceptibility testing. Eur Respir J. 2023;62(5).