Results and lessons learned from implementing modified shorter treatment regimens (mSTR) for MDR/RR-TB under operational research conditions

Dr Askar Yedilbayev
Joint Infectious Diseases Unit
WHO Regional Office for Europe

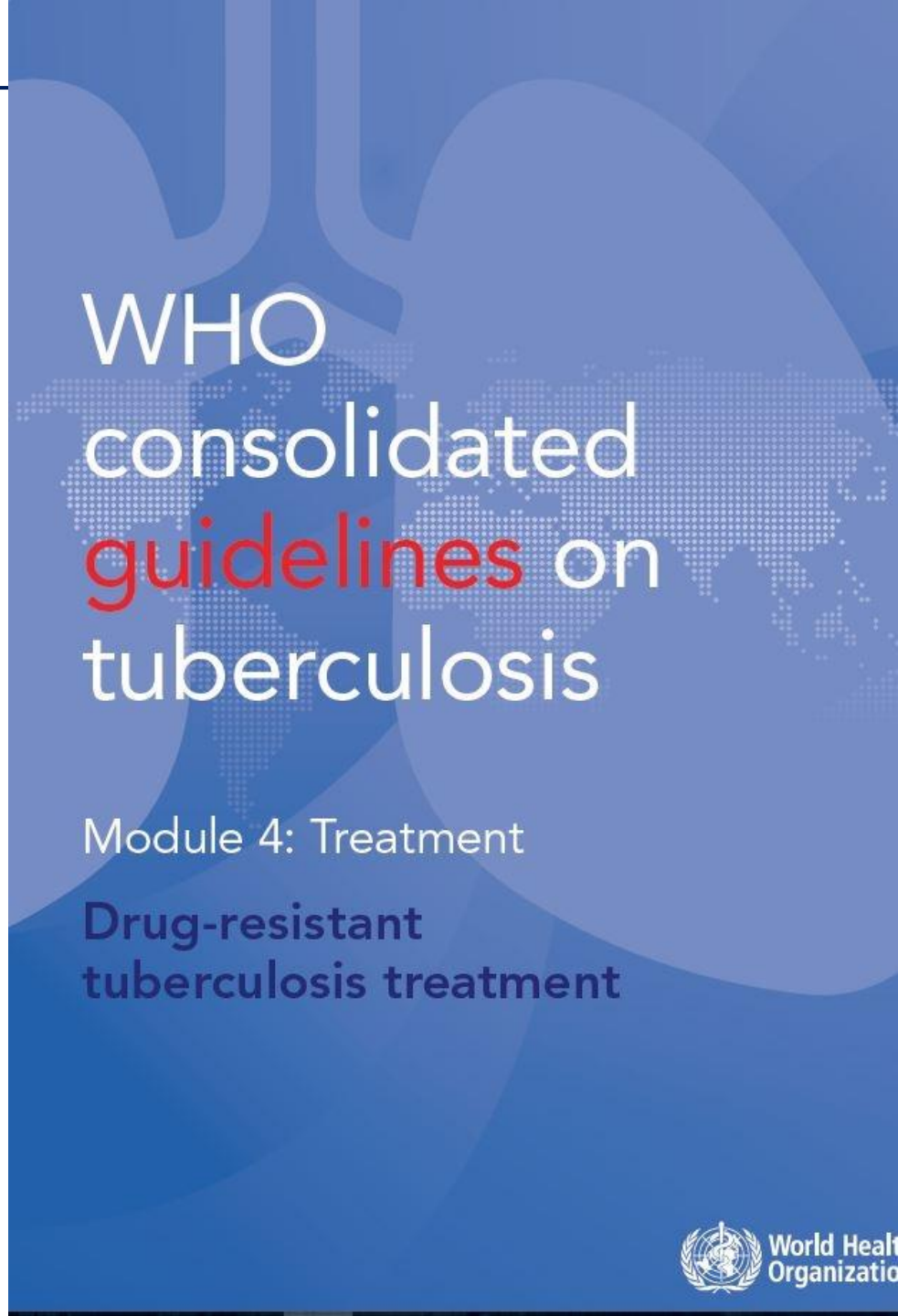
World Health Organization
European Region

2020 WHO Guidelines
Shorter all-oral bedaquiline-containing regimen for MDR/RR-TB

4-6 Bdq (6m) – Lfx – Cfz – Eto – Z – E - Hh / 5 Lfx – Cfz – Z - E

2.1 A shorter all-oral bedaquiline-containing regimen of 9-12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant TB (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded (*Conditional recommendation, very low certainty in the evidence*).

World Health Organization
European Region



Treatment regimens

In this study, three all-oral shorter RR-TB treatment regimens are proposed, based on knowledge of their safety and efficacy as of 2020.

Regimen 1: 39 weeks Lfx + Bdq + Lzd + Cfz + Cs

Regimen 2: 39 weeks Lfx + Bdq + Lzd + Cfz + Dlm

Treatment regimen 1 is preferred as it includes all Group A and Group B anti-TB drugs. In patients with suspected resistance or intolerance of Cs, regimen 2 should be considered as primary choice of therapy.

For children under 6 years of age:

Regimen 3: 39 weeks Lfx + Dlm + Lzd + Cfz

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

World Health Organization
European Region

Operational research objectives

- **Primary objective:**
  - To determine the treatment outcomes of patients who are treated with novel (modified) shorter MDR-TB regimen
- **Secondary objectives:**
  - To assess the safety of a novel (modified) shorter MDR-TB regimen through rates of adverse events
  - To determine the proportion of patients with recurrence during 12 months after successful treatment with a novel (modified) shorter MDR-TB regimen

Photo: First patient starting mSTR in Republic on Moldova, September 2020

World Health Organization
European Region

Benefits of OR on mSTR for MDR-TB

- Increased coverage of patients with potentially safer and effective regimens
- Increased treatment success rate and decreases LTFU rates and rates of other unfavorable outcomes
- Promotion of good clinical care and simplifies treatment monitoring schedule
- Health system strengthening through reduction of hospitalization costs, promotion of patient-centered models of care and capacity building
- Decreased risk for nosocomial transmission of infection
- Contributes to the reduction of stigma and the decrease of household costs due to disability
- Faster impact on TB epidemic in the Region

World Health Organization
European Region

mSTRs: six times less pill burden for patients

Standard treatment regimen for DR-TB (before 2019)

- 24 months
- 14 600 pills
- 280 daily injections

Fully-oral standard treatment regimen for DR-TB (2020)

- 18-20 months
- 4 500 pills
- 0 injections

x3 times lower pill burden

Fully-oral modified shorter treatment regimen for DR-TB

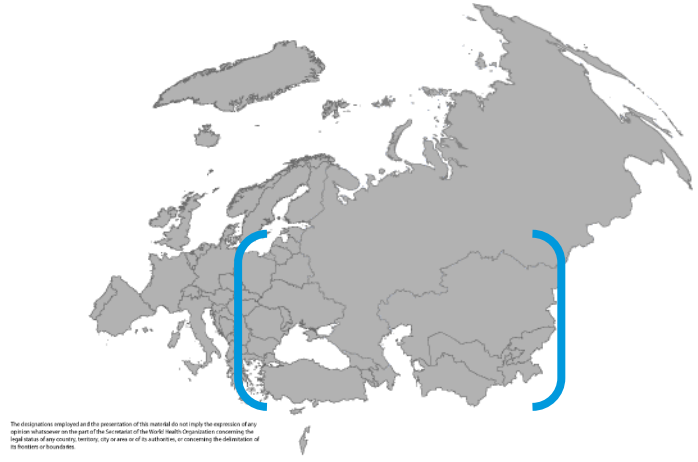
- 9 months
- 2 300 pills
- 0 injections

x2 times lower pill burden

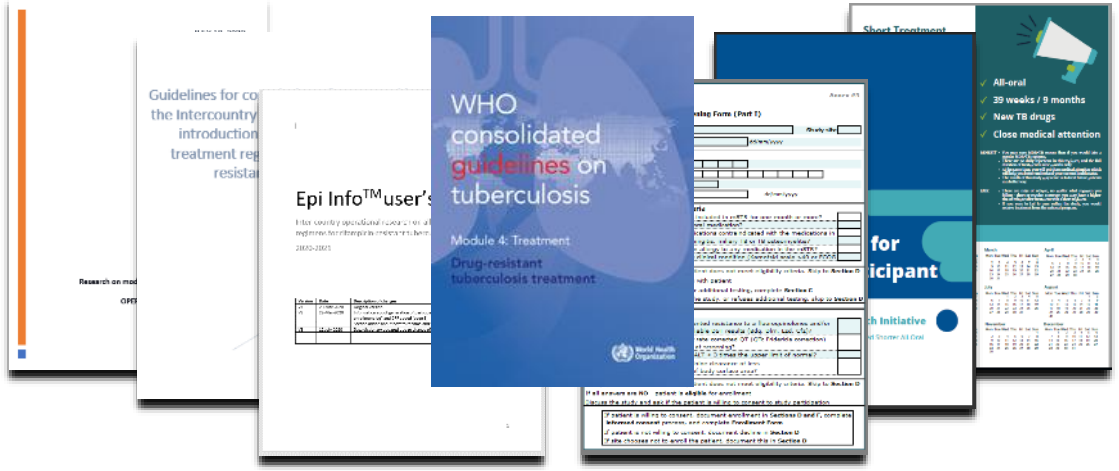
World Health Organization
European Region

Regional OR on mSTR implementation: highlights

13 high-priority countries of WHO European Region



Regional Operational Research Package in line with WHO guidelines on DR-TB



Ensuring people-centeredness of service delivery

9 months

All-oral

6 times lower pill burden

Progress in the implementation of the new Regional initiative

- **2813 patients** were initiated on mSTR as the Regional cohort in 13 countries
- National mSTR cohorts have been established in all 13 countries; as of 30 September 2023, **over 5000 more patients** were enrolled
- The WHO Regional Office for Europe advised countries to continue enrollment in the mSTR national cohorts of children under 14 years of age and pregnant women who don't meet eligibility criteria for BPaL(M)

Treatment and follow-up monitoring schedule

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Until end of treatment	End of treatment	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
Clinical evaluation														
Vital signs	×		×	×	×	×	×	×	Monthly	×	×	×	×	×
Brief peripheral neuropathy screen	×		×	×	×	×	×	×	Monthly	×				×
Visual acuity and colorblindness screen	×		×	×	×	×	×	×	Monthly	×				×
Post-end-of- treatment consultation										×	×	×	×	×
Assessment and follow-up of adverse events	×	×	×	×	×	×	×	×	At each scheduled /unscheduled visit	×	×	×	×	×
Weight	×	×	×	×	×	×	×	×	Monthly	×	×	×	×	×
Bacteriological testing														
Smear	×		×	×	×	×	×	×	Monthly	×		×		×
Culture	×		×	×	×	×	×	×	Monthly	×		×		×
Freeze baseline culture	×													
Xpert MTB/RIF	×													
LPA (Hain GenoType MTBDRsl)	×			If smear- or culture-positive check for amplification of resistance										
Culture-based first-line DST	×			If smear- or culture-positive check for amplification of resistance										
Culture-based second-line DST	×			If smear- or culture-positive check for amplification of resistance										

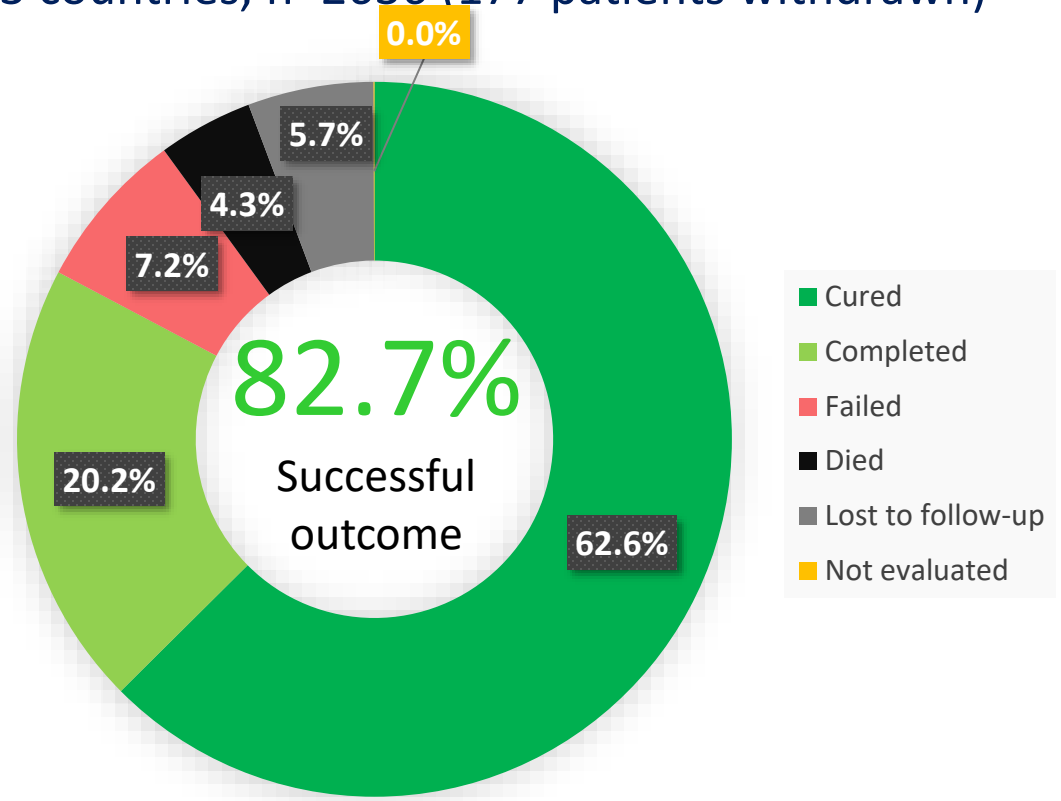
	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Until end of treatment	End of treatment	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
Laboratory testing														
ECG	×	×	×	×	×	×	×	×	Monthly	×	×	×		
Full blood count (hemoglobin, red blood cells. white blood cells and platelets) if on Lzd	×		×	×	×	×	×	×	Monthly (if on Lzd)	×				
Liver function tests (AST, ALT)	×		×	×	×	×	×	×	Monthly	×				
Serum creatinine	×		×	×	×	×	×	×	Monthly	×				
Serum potassium	×		×	×	×	×	×	×	Monthly	×				
Hepatitis Bs Antigen	×													
Hepatitis C Antibody	×													
HbA1c	×		Repeated every 3 months if elevated											
COVID-19 PCR	×		At baseline and then only if clinically indicated											
Pregnancy test (females)	×													
HIV testing	×													
CD4 (repeated every 6 months if HIV+)	×							×						
HIV Viral load (repeated every 6 months if HIV +)	×							×						
Chest X-Ray	×							×		×				

- Implementation of all-oral mSTR is not complicated and very similar to the standard conditions of good PMDT;
- Ensure effectiveness and safety of new regimens;
- Improve good clinical care of patients;
- Increase capacity of clinicians.

World Health Organization
European Region

Outcomes upon treatment completion

13 countries, n=2636 (177 patients withdrawn)

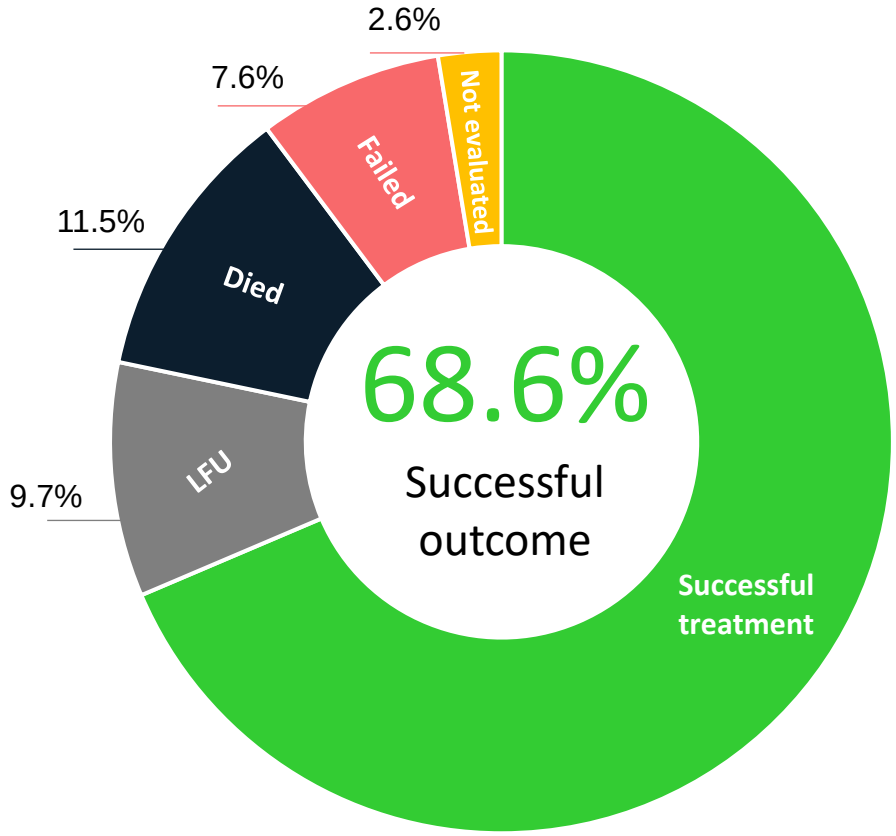


World Health Organization
European Region

n=2636: out of 2813 patients included in the Regional cohort;
1 subject was missing final treatment outcome;
177 (6%) patients were withdrawn from the study without fulfilling treatment failed definition;
Patients that failed to receive at least 246, but no more than 300 doses, of mSTR regimen within 245 to 301 days regardless of the reason were classified as failure, though programmatically could have satisfied the definition of cured or treatment completed

MDR/RR-TB outcomes

12 countries*; 2019 cohort; n=20145**

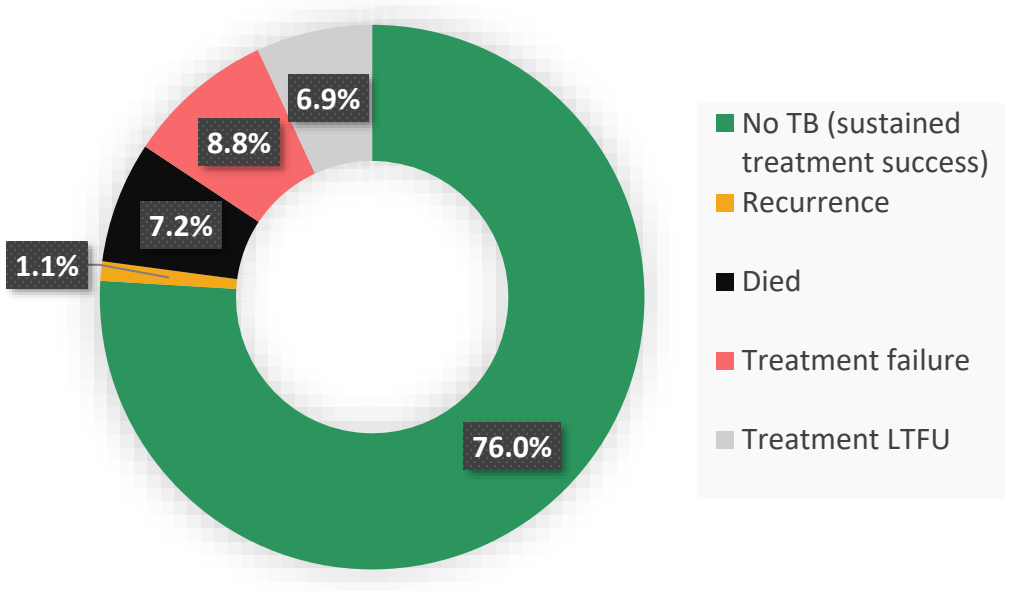


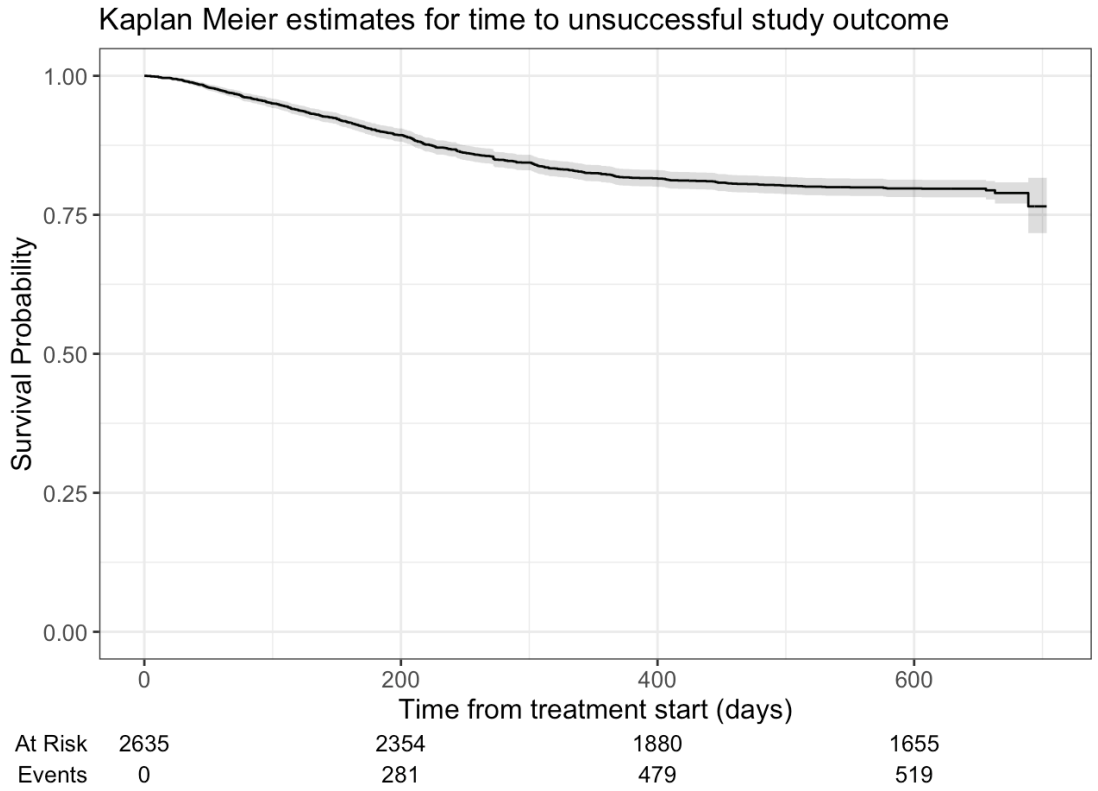
Source: WHO Global TB database

*Latvia did not report data
**Patients with an outcome 'Not evaluated' were excluded

Preliminary results of 12-month post-treatment follow-up (mSTR)

n=2171, as of 30 June 2023 in total 25 cases of recurrence and 44 deaths were registered during 12-month follow-up period; 264 patients were still at the final months of 12-month follow-up and 196 were not evaluated (both groups excluded as not evaluated), which lead to somewhat overestimated unsuccessful final study outcome

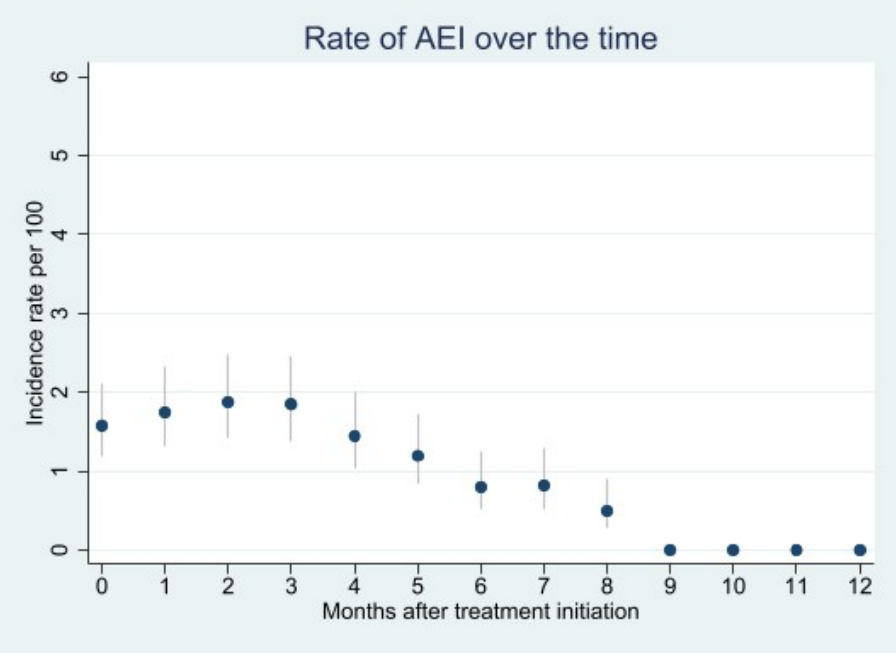




World Health Organization
European Region

Safety: Occurrence of AEI of grade 3 and higher by months and types

301 AEIs were observed during study treatment among 252 participants (9%), reaching the rate of 1.32 per 100 P-M;
7.5% patients had one incidence of SAE, 1.3% - two or more



Frequency and type of AEI during treatment (in % of all and in per person-month)

AEI term	Number	%	Rate	95% CI
Peripheral neuropathy	32	10.6	0.14	(0.10-0.20)
Myelosuppression	157	52.2	0.69	(0.59-0.80)
QT interval prolongation	49	16.3	0.21	(0.16-0.28)
Hepatitis	25	8.3	0.11	(0.74-0.16)
Optic neuritis	16	5.3	0.07	(0.04-0.11)
Hypokalemia	7	2.3	0.03	(0.01-0.06)
Acute kidney inj.	15	5.0	0.07	(0.04-0.11)
Total	**301**	**100**	**1.32**	**(1.18-1.48)**

World Health Organization
European Region

Publications on mSTR

IJTLD OPEN 1(3):103–110
http://dx.doi.org/10.5588/ijtldopen.24.0035

VIEWPOINT

Operational research as a mechanism to improve treatment outcomes for drug-resistant TB in the WHO European Region

G.B. Migliori,[1] O. Korotych,[2] J. Achar,[3,4] A. Ciobanu,[2] G. Dravniece,[5] M. Germanovych,[2] E. Gurbanova,[6] A. Hovhannesyan,[2] N. Khachatryan,[7] L. Kuksa,[8] N. Lomtadze,[9,10] M.L. Rich,[11] A. Skrahina,[12] A. Yedilbayev[2]

[1]Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri, Istituto di Ricovero e Cura a Carattere Scientifico, Tradate, Italy; [2]Joint Infectious Diseases Unit, World Health Organization Regional Office for Europe, Copenhagen, Denmark; [3]Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden; [4]Department of Science and Innovation–National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research, South Africa Medical Research Council Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [5]PATH, Kyiv, Ukraine; [6]Lung Clinic, University of Tartu, Tartu, Estonia; [7]National Center of Pulmonology, Ministry of Health, Abovyan, Armenia; [8]Tuberculosis and Lung Disease Clinic, Riga East University Hospital, Riga, Latvia; [9]National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia; [10]The University of Georgia, Tbilisi, Georgia, [11]Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; [12]Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus

SUMMARY

In 2022, the WHO European Region accounted for 15.1% of all incident rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB) cases. Most occurred in 18 high-priority countries of eastern Europe and central Asia, many of which joined an initiative led by the WHO Regional Office for Europe. The aim was to introduce three, fully oral, 9-month modified shorter treatment regimens (mSTR) to treat RR/MDR-TB under operational research conditions. The three regimens were: 1) bedaquiline + linezolid + levofloxacin + clofazimine + cycloserine (BdqLzdLfxCfxCs); 2) BdqLzdLfxCfz + delamanid (Dlm) for children over 6 years of age and adults; and 3) DlmLzdLfxCfz for children under 6 years of age. The project aimed to enhance treatment success, facilitate mSTR implementation, promote quality of care and build research capacity, while also contributing to global knowledge on all-oral mSTR use. Between April 2020 and June 2022, >2,800 patients underwent mSTR treatment in the WHO European Region. This unique experience promoted further collaboration with national tuberculosis programmes, health authorities, experts and donors within and outside Europe, with a focus on implementing operational research and improving the quality of care in high TB burden countries of the region. In the hope of encouraging others to adopt this model, we have described the principles of the initiative, its strengths and weaknesses and next steps.

KEY WORDS: tuberculosis; MDR-TB; shorter regimens; rifampicin resistant; mSTR

In 2022, the WHO estimated that about 410,000 rifampicin resistant (RR)/multidrug-resistant TB (MDR-TB) cases occurred globally, which constitutes 3.9% of the global TB burden.[1] The proportion of RR/MDR-TB was 3.3% among new and 17% among previously treated cases.[1] Although the WHO European Region accounted for only 2.2% of the global TB burden (the regional incidence rate per 100,000 population was 2.5 against 208 globally), it had 15.1% of all incident RR/MDR-TB cases. The estimated prevalence of RR/MDR-TB was 24% among new and 54% among previously treated cases.[1] The management of RR/MDR-TB patients is clinically challenging due to the complexity of its diagnosis, the long treatment duration, frequency of adverse events and the higher cost of second-line drugs.[2]

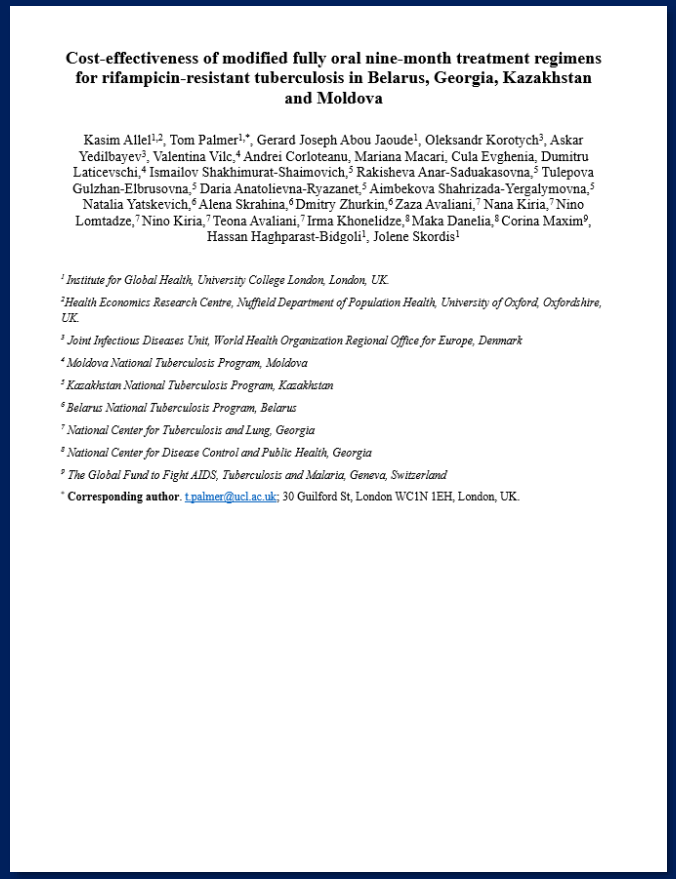
In the WHO European Region, approximately half of incident RR/MDR-TB cases are diagnosed: with 34,630 notified cases vs. an estimated number of 61,500. Most (85%) incident TB cases occur in 18 countries of eastern Europe and central Asia, which are referred to as high-priority countries[3] in the WHO European Region.[4] Of these 18 high-priority countries, 13 (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Tajikistan, Turkmenistan, Ukraine and Uzbekistan) joined the WHO European Regional initiative to introduce a fully oral, modified shorter treatment regimen (mSTR) for RR/MDR-TB under operational research (OR) conditions (Figure 1). In 2019 (prior to the study), the combined treatment success rate for RR/MDR-TB (excluding pre-extensively drug-resistant TB [pre-XDR-TB] and XDR-TB) was 68.6%, which is significantly lower than the 80% regional milestone for 2025 according to the

GBM, OK and AY contributed equally.

Correspondence to: Oleksandr Korotych, World Health Organization Regional Office for Europe, Marmorvej 51, DK-2100 Copenhagen, Denmark. E-mail: korotycho@who.int

Article submitted 23 January 2024. Final version accepted 7 February 2024.

On process and implementation @ International Journal of Tuberculosis and Lung Diseases



Cost-effectiveness of modified fully oral nine-month treatment regimens for rifampicin-resistant tuberculosis in Belarus, Georgia, Kazakhstan and Moldova

Kasim Allel[1,2], Tom Palmer[1,*], Gerard Joseph Abou Jaoude[1], Oleksandr Korotych[3], Askar Yedilbayev[3], Valentina Vilc,[4] Andrei Corloteanu, Mariana Macari, Cula Evghenia, Dumitru Laticevschi,[4] Ismailov Shakhimurat-Shaimovich,[5] Rakisheva Anar-Saduakasovna,[5] Tulepova Gulzhan-Elbrusovna,[5] Daria Anatolievna-Ryazanet,[5] Aimbekova Shahrizada-Yergalymovna,[5] Natalia Yatskevich,[6] Alena Skrahina,[6] Dmitry Zhurkin,[6] Zaza Avaliani,[7] Nana Kiria,[7] Nino Lomtadze,[7] Nino Kiria,[7] Teona Avaliani,[7] Irma Khonelidze,[8] Maka Danelia,[8] Corina Maxim[9], Hassan Haghparast-Bidgoli[1], Jolene Skordis[1]

[1] *Institute for Global Health, University College London, London, UK.*

[2] *Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxfordshire, UK.*

[3] *Joint Infectious Diseases Unit, World Health Organization Regional Office for Europe, Denmark*

[4] *Moldova National Tuberculosis Program, Moldova*

[5] *Kazakhstan National Tuberculosis Program, Kazakhstan*

[6] *Belarus National Tuberculosis Program, Belarus*

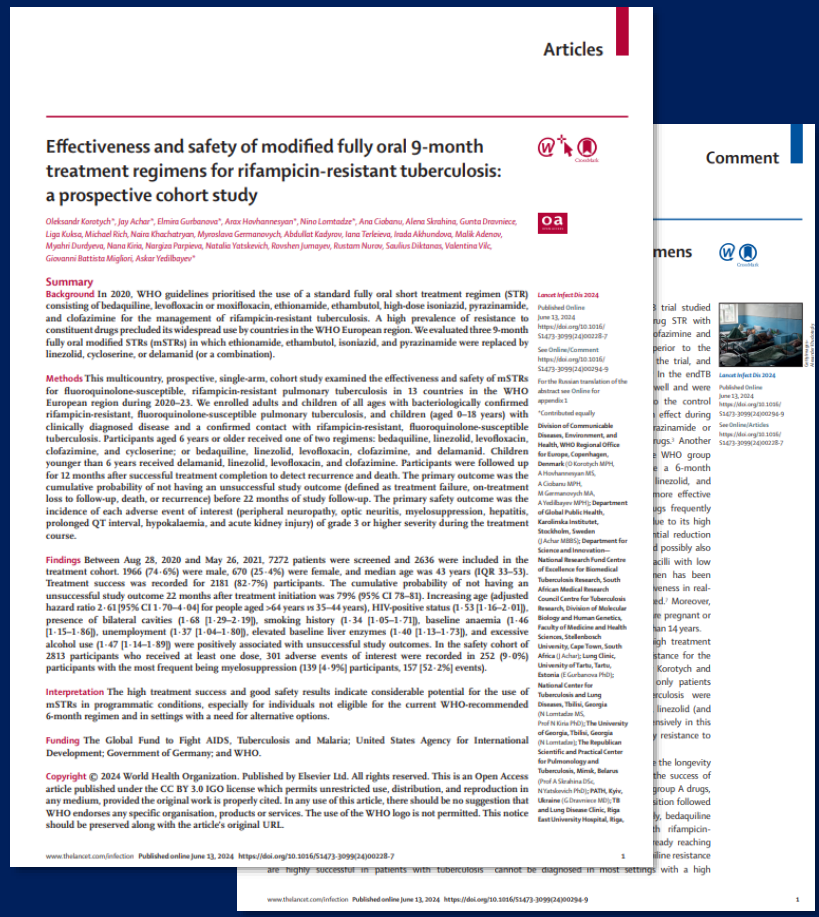
[7] *National Center for Tuberculosis and Lung, Georgia*

[8] *National Center for Disease Control and Public Health, Georgia*

[9] *The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland*

[*] **Corresponding author**. t.palmer@ucl.ac.uk; 30 Guilford St, London WC1N 1EH, London, UK.

Publication on cost-effectiveness of mSTR OR @ Lancet Global Health*



Articles

Effectiveness and safety of modified fully oral 9-month treatment regimens for rifampicin-resistant tuberculosis: a prospective cohort study

Oleksandr Korotych*, Jay Achar*, Elmira Gurbanova*, Anzx Hovhannesyan*, Nino Lomtadze*, Ana Ciobanu, Alena Skrahina, Gunta Dravniece, Liga Kuksa, Michael Rich, Naira Khachatryan, Myroslava Germanovych, Abdullat Kadyrov, Iana Terleieva, Irada Akhundova, Malik Adenov, Myahri Durdyeva, Nana Kiria, Nargiza Parpieva, Natalia Yatskevich, Rovshen Jumayev, Rustam Nurov, Saulius Diktanas, Valentina Vilc, Giovanni Battista Migliori, Askar Yedilbayev*

Summary

Background In 2020, WHO guidelines prioritised the use of a standard fully oral short treatment regimen (STR) consisting of bedaquiline, levofloxacin or moxifloxacin, ethionamide, ethambutol, high-dose isoniazid, pyrazinamide, and clofazimine for the management of rifampicin-resistant tuberculosis. A high prevalence of resistance to constituent drugs precluded its widespread use by countries in the WHO European region. We evaluated three 9-month fully oral modified STRs (mSTRs) in which ethionamide, ethambutol, isoniazid, and pyrazinamide were replaced by linezolid, cycloserine, or delamanid (or a combination).

Methods This multicountry, prospective, single-arm, cohort study examined the effectiveness and safety of mSTRs for fluoroquinolone-susceptible, rifampicin-resistant pulmonary tuberculosis in 13 countries in the WHO European region during 2020–23. We enrolled adults and children of all ages with bacteriologically confirmed rifampicin-resistant, fluoroquinolone-susceptible pulmonary tuberculosis, and children (aged 0–18 years) with clinically diagnosed disease and a confirmed contact with rifampicin-resistant, fluoroquinolone-susceptible tuberculosis. Participants aged 6 years or older received one of two regimens: bedaquiline, linezolid, levofloxacin, clofazimine, and cycloserine; or bedaquiline, linezolid, levofloxacin, clofazimine, and delamanid. Children younger than 6 years received delamanid, linezolid, levofloxacin, and clofazimine. Participants were followed up for 12 months after successful treatment completion to detect recurrence and death. The primary outcome was the cumulative probability of not having an unsuccessful study outcome (defined as treatment failure, on-treatment loss to follow-up, death, or recurrence) before 22 months of study follow-up. The primary safety outcome was the incidence of each adverse event of interest (peripheral neuropathy, optic neuritis, myelosuppression, hepatitis, prolonged QT interval, hypokalaemia, and acute kidney injury) of grade 3 or higher severity during the treatment course.

Findings Between Aug 28, 2020 and May 26, 2021, 7272 patients were screened and 2636 were included in the treatment cohort. 1966 (74·6%) were male, 670 (25·4%) were female, and median age was 43 years (IQR 33–53). Treatment success was recorded for 2181 (82·7%) participants. The cumulative probability of not having an unsuccessful study outcome 22 months after treatment initiation was 79% (95% CI 78–81). Increasing age (adjusted hazard ratio 2·61 [95% CI 1·70–4·04] for people aged >64 years vs 35–44 years), HIV-positive status (1·53 [1·16–2·01]), presence of bilateral cavities (1·68 [1·29–2·19]), smoking history (1·34 [1·05–1·71]), baseline anaemia (1·46 [1·15–1·86]), unemployment (1·37 [1·04–1·80]), elevated baseline liver enzymes (1·40 [1·13–1·73]), and excessive alcohol use (1·47 [1·14–1·89]) were positively associated with unsuccessful study outcomes. In the safety cohort of 2813 participants who received at least one dose, 301 adverse events of interest were recorded in 252 (9·0%) participants with the most frequent being myelosuppression (139 [4·9%] participants, 157 [52·2%] events).

Interpretation The high treatment success and good safety results indicate considerable potential for the use of mSTRs in programmatic conditions, especially for individuals not eligible for the current WHO-recommended 6-month regimen and in settings with a need for alternative options.

Funding The Global Fund to Fight AIDS, Tuberculosis and Malaria; United States Agency for International Development; Government of Germany; and WHO.

Comment

Publication on effectiveness and safety of mSTR @ Lancet Infectious Diseases and commentaries from editors

* Pre-print article

Publications on mSTI

IJTLD OPEN 1(3):103–110
http://dx.doi.org/10.5588/ijtldopen.24.0035

VIEWPOINT

Operational research as a mechanism to improve treatment outcomes for drug-resistant TB in the WHO European Region

G.B. Migliori,[1] O. Korotych,[2] J. Achar,[3,4] A. Ciobanu,[2] G. Dravniece,[5] M. Germanovych,[2] E. Gurbanova,[6] A. Hovhannesyan,[2] N. Khachatryan,[7] L. Kuksa,[8] N. Lomtadze,[9,10] M.L. Rich,[11] A. Skrahina,[12] A. Yedilbayev[2]

[1]Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri, Istituto di Ricovero e Cura a Carattere Scientifico, Tradate, Italy; [2]Joint Infectious Diseases Unit, World Health Organization Regional Office for Europe, Copenhagen, Denmark; [3]Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden; [4]Department of Science and Innovation–National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research, South Africa Medical Research Council Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [5]PATH, Kyiv, Ukraine; [6]Lung Clinic, University of Tartu, Tartu, Estonia; [7]National Center of Pulmonology, Ministry of Health, Abovyan, Armenia; [8]Tuberculosis and Lung Disease Clinic, Riga East University Hospital, Riga, Latvia; [9]National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia; [10]The University of Georgia, Tbilisi, Georgia, [11]Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; [12]Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus

SUMMARY

In 2022, the WHO European Region accounted for 15.1% of all incident rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB) cases. Most occurred in 18 high-priority countries of eastern Europe and central Asia, many of which joined an initiative led by the WHO Regional Office for Europe. The aim was to introduce three, fully oral, 9-month modified shorter treatment regimens (mSTR) to treat RR/MDR-TB under operational research conditions. The three regimens were: 1) bedaquiline + linezolid + levofloxacin + clofazimine + cycloserine (BdqLzdLfxCfxCs); 2) BdqLzdLfxCfz + delamanid (Dlm) for children over 6 years of age and adults; and 3) DlmLzdLfxCfz for children under 6 years of age. The project aimed to enhance treatment success, facilitate mSTR implementation, promote quality of care and build research capacity, while also contributing to global knowledge on all-oral mSTR use. Between April 2020 and June 2022, >2,800 patients underwent mSTR treatment in the WHO European Region. This unique experience promoted further collaboration with national tuberculosis programmes, health authorities, experts and donors within and outside Europe, with a focus on implementing operational research and improving the quality of care in high TB burden countries of the region. In the hope of encouraging others to adopt this model, we have described the principles of the initiative, its strengths and weaknesses and next steps.

KEY WORDS: tuberculosis; MDR-TB; shorter regimens; rifampicin resistant; mSTR

In 2022, the WHO estimated that about 410,000 rifampicin resistant (RR)/multidrug-resistant TB (MDR-TB) cases occurred globally, which constitutes 3.9% of the global TB burden.[1] The proportion of RR/MDR-TB was 3.3% among new and 17% among previously treated cases.[1] Although the WHO European Region accounted for only 2.2% of the global TB burden (the regional incidence rate per 100,000 population was 2.5 against 208 globally), it had 15.1% of all incident RR/MDR-TB cases. The estimated prevalence of RR/MDR-TB was 24% among new and 54% among previously treated cases.[1] The management of RR/MDR-TB patients is clinically challenging due to the complexity of its diagnosis, the long treatment duration, frequency of adverse events and the higher cost of second-line drugs.[2]

In the WHO European Region, approximately half of incident RR/MDR-TB cases are diagnosed: with 34,630 notified cases vs. an estimated number of 61,500. Most (85%) incident TB cases occur in 18 countries of eastern Europe and central Asia, which are referred to as high-priority countries[3] in the WHO European Region.[4] Of these 18 high-priority countries, 13 (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Tajikistan, Turkmenistan, Ukraine and Uzbekistan) joined the WHO European Regional initiative to introduce a fully oral, modified shorter treatment regimen (mSTR) for RR/MDR-TB under operational research (OR) conditions (Figure 1). In 2019 (prior to the study), the combined treatment success rate for RR/MDR-TB (excluding pre-extensively drug-resistant TB [pre-XDR-TB] and XDR-TB) was 68.6%, which is significantly lower than the 80% regional milestone for 2025 according to the

GBM, OK and AY contributed equally.

Correspondence to: Oleksandr Korotych, World Health Organization Regional Office for Europe, Marmorvej 51, DK-2100 Copenhagen, Denmark. E-mail: korotycho@who.int

Article submitted 23 January 2024. Final version accepted 7 February 2024.

On process and implementation @ International Journal of Tuberculosis and Lung Diseases

WHO operational handbook on tuberculosis

Module 4: treatment and care

World Health Organization

Articles

…ness and safety of modified fully oral 9-month …t regimens for rifampicin-resistant tuberculosis: …tive cohort study

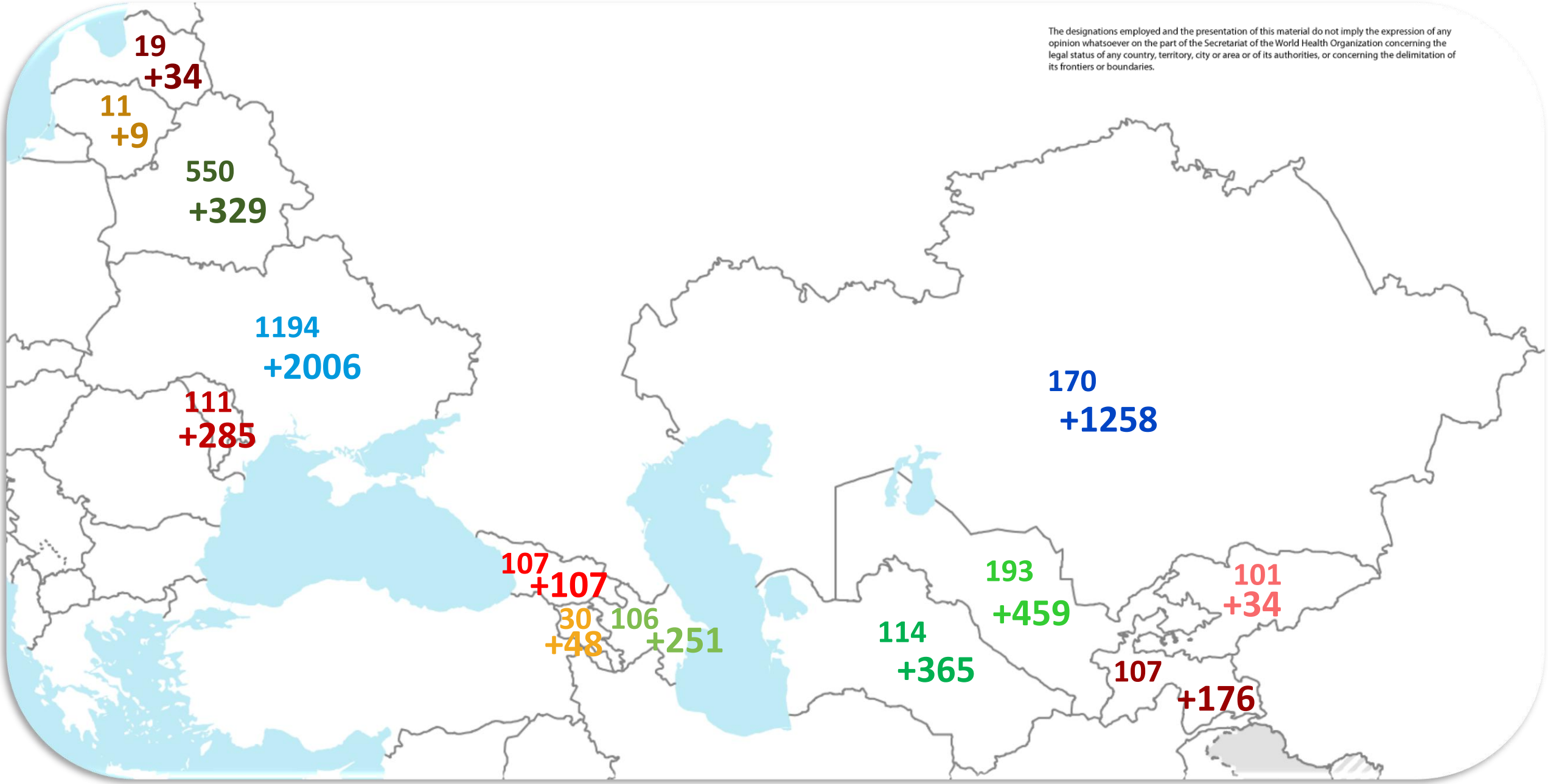
Comment

…mens

Publication on effectiveness and safety of mSTR @ Lancet Infectious Diseases and commentaries from editors

* Pre-print article

Geographic distribution – regional + national cohorts



Conclusions

- mSTR regimens show promising results and have a potential to facilitate achieving the regional target of 80% success rate for MDR/RR-TB by 2025
- 12-month post-treatment recurrence rate is low (1.1%)
- Analysis of predictors of unsuccessful outcomes suggest that DR-TB outcomes can be improved further, if specific attention is given to reducing alcohol dependence and smoking, ensuring proper nutrition and management of anemia, providing social support and patient-centred care to elderly and unemployed; providing enhanced care and treatment monitoring to patients with HIV and elevated liver enzymes; ensuring early diagnosis of TB
- Proportion of patients experiencing SAE or AEI is generally low, however it is important to prioritize clinical monitoring and care for patients with pre-existing conditions, as well as to ensure adequate management of those conditions to prevent SAE and AEI, particularly: HIV, viral Hepatitis C, heart diseases, anemia, peripheral neuropathy, increased creatinine and liver enzymes, malnutrition, decreased neutrophil count
- This initiative also helped lay the groundwork for the effective implementation of WHO-recommended shorter DR-TB treatment regimens introduced in 2022 and 2025.

World Health Organization
European Region

Once again, we thank everyone involved!

In case of questions, please contact:
eurotb@who.int

World Health Organization
European Region