Assessment of country's preparedness to introduction of BPaL(M) into the programmatic practice

World Health Organization
European Region

Nino Lomtadze, M.D., MSc
Consultant (mSTR, rGLC), WHO/Euro

20th webinar of the Virtual Medical Consilium (VMC)

Questionnaire for Assessment of the Implementation Scenarios of the BPaLM regimen

World Health Organization
REGIONAL OFFICE FOR Europe

To understand different scenarios for introduction and implementation of novel 6-month treatment regimens (BPaLM and BPaL) for MDR/RR-TB or pre-XDR-TB under routine programmatic conditions in high TB priority countries of the WHO European Region, the WHO Regional Office developed and launched a questionnaire that is structured around five programmatic areas:

- ✓ National treatment policy
- ✓ Service delivery
- ✓ Drug supply and management
- ✓ Laboratory diagnosis
- ✓ Monitoring and evaluation

Learning on different implementation can inform:

a) WHO and other international partners and funding institutions (Stop TB Partnership/GDF, the Global Fund) to better plan the country tailored technical or financial assistance, make relevant planning and needs forecasting for drugs and consumables at the global level and better inform future policy

b) NTPs to revisit existing challenges and reinforce further solutions

Sub-group of mSTR task force on introduction of novel 6-month regimens

Checklist for country preparedness and planning

04.08.2022

Novel 6-month treatment regimens for treatment of MDR/RR-TB or pre-XDR-TB

Checklist for country preparedness and planning

In May 2002, World Health Organization (WHO) issued rapid communication[1] to inform National Tuberculosis Programmes (NTPs) and other stakeholders about the available new evidence on treatment of drug-resistant tuberculosis (DR-TB) that will be presented in a 2022 update of the WHO consolidated guidelines. Part of the new evidence concerns treatment of multidrug-resistant (MDR) TB, rifampicin-resistant (RR) TB, extensively drug resistant (XDR) TB or pre-XDR-TB2 patients with novel 6-month regimens comprising bedaquiline, pretomanid and linezolid with or without moxifloxacin (BPaL(M).

The recommendations in the upcoming WHO guidelines will have implications for the management of DR-TB. In order to allow for rapid transition and planning at country level the current checklist for preparedness and planning has been developed. The checklist is not exhaustive, meant to be a reminder of issues to be considered by the implementation site(s).

The secretariat of the WHO/EURO Sub-Group on Novel 6-month Regimens is ready to offer additional resources or technical assistance to countries in case there is a need to develop a detailed programmatic implementation guide. The possible examples include the KNCV Tuberculosis Foundation guide[3] for introduction of new drugs and shorter regimens.

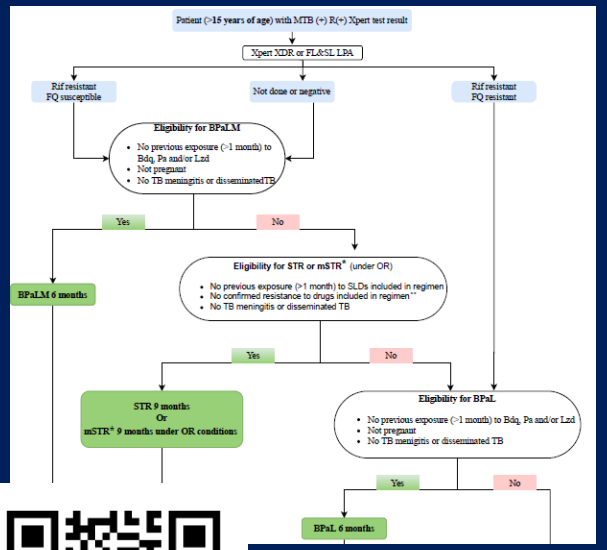
BACKGROUND INFORMATION
Collect background information on TB and DR-TB burden in the country including: - Total notified TB cases per year (number, notification rate) - Pulmonary TB: o Total pulmonary TB cases per year (number, notification rate) o Total bacteriologically confirmed pulmonary TB cases per year (number) o Total pulmonary bacteriologically confirmed MDR/RR-TB cases per year (number) o Pulmonary MDR/RR-TB patients younger than 15 years of age (number) o Total bacteriologically confirmed pulmonary previously treated MDR/RR-TB patients per year (number) - Extrapulmonary TB: o Total extrapulmonary TB cases per year (number, notification rate) o Total extrapulmonary bacteriologically confirmed MDR/RR-TB cases per year (number) o Total extrapulmonary MDR/RR-TB patients younger than 15 years of age (number) o Total bacteriologically confirmed extrapulmonary previously treated MDR/RR-TB patients per year (number)

[1] Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2022 (WHO/UCN/TB/2022.2). License: CC BY-NC-SA 3.0 IGO.
[2] New definitions agreed by the WHO consultation in October 2020: pre-XDR-TB: TB caused by *Mycobacterium tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone; XDR- TB: TB caused by M. tuberculosis strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug.
[3] KNCV Tuberculosis Foundation. Funded by USAID/Challenge TB. Generic programmatic and clinical guide for the introduction of new drugs and shorter regimen for treatment of Multi/Extensively Drug- Resistant Tuberculosis. 2017

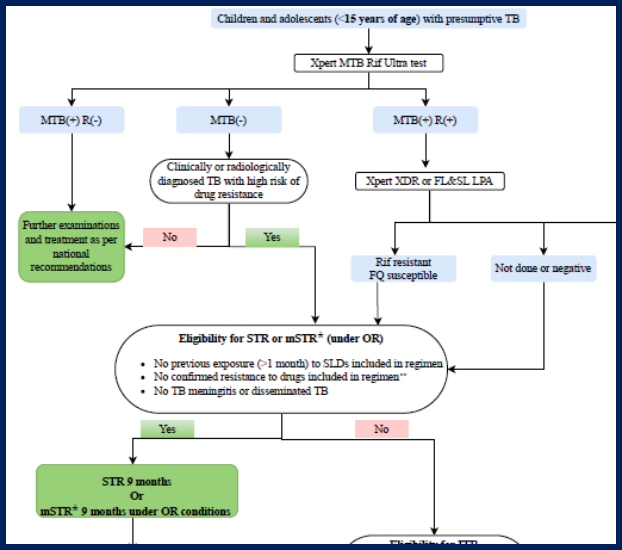
- Testing coverage to group A and B anti-DR-TB drugs: o Testing coverage to fluoroquinolones (Fq) among all pulmonary bacteriologically confirmed MDR/RR-TB cases (number, %) o Resistance to Fq among all bacteriologically confirmed pulmonary MDR/RR-TB cases (number, %) o Resistance to Fq among bacteriologically confirmed pulmonary previously treated MDR/RR-TB cases (number, % of all bacteriologically confirmed previously treated pulmonary MDR/RR-TB cases) o Information on resistance to bedaquiline (Bdq), linezolid (Lzd), delamanid (Dlm) and pretomanid (Pa) among pulmonary bacteriologically confirmed MDR/RR-TB cases would be an asset
Collect background information on TB case management at country level, such as possibility for directly observed treatment (DOT) for seven days per week employing different modalities, among others Digital Adherence Technologies
Ensure appropriate social support for patients
Identify technical assistance partners
REGULATORY FRAMEWORK
Review national regulatory environment considering use of BPaL(M). Consider amendments if necessary. Describe steps and timeline needed for amendments
Revise national policies and guidelines as required
ADMINISTRATEMENT
Prepare and conduct meetings with representatives of the National TB Programme (NTP), key stakeholders and Partners for introduction of BPaL (M)
Consider setting up technical working group (TWG), in case such does not exist, in order to follow the progress of BPaL(M) use in the country
Consider developing implementation plan and budget for BPaL(M) implementation (revise the activity and implementation plan of the NTP as necessary)
Identify clinical centres for implementation of BPaL(M)
CAPACITY BUILDING
Ensure the availability of human resources (laboratory, clinical management, supervision) necessary for launching BPaL(M)
Develop standard operational procedures (SOP) for treatment adherence support where necessary
Develop training material for service providers (doctors, nurses, laboratory personnel, supervisors, national pharmacovigilance centre (PV) staff)
Develop educational materials for patients and their supporters
Conduct inter-disciplinary capacity building activities for teams involved in service delivery on: new diagnostic algorithms, SOPs, monitoring and evaluation teams (M&E) etc.
DRUG MANAGEMENT
Review the existing drug management system. Consider amendments in order to ensure uninterrupted supply of drugs for BPaL(M) treatment regimen
Ensure forecasting and quantification considering BPaL(M)
Consider import waiver or registration of the new drugs as necessary
Ensure a drug management system to monitor stock status considering BPaL(M)

Proposed triage algorithms for patients under and over 15 years of age for WHO European Region

15 years and older



Under 15 years



Results: Countries

Six countries participated, 5 of which belong to the WHO list of high MDR-TB burden countries (listed in alphabetical order):

- ❑Belarus
- ❑Georgia
- ❑Kyrgyz Republic
- ❑Republic of Moldova
- ❑Ukraine
- ❑Uzbekistan

Results: National Treatment Guidelines and Policy

World Health Organization
REGIONAL OFFICE FOR Europe

Country	Recommendations on implementation of modified Short Treatment Regimens (mSTR) for MDR/RR-TB patients without resistance to Fluoroquinolones (6/6 100% -Yes)	Recommendations on implementation of 6–9 months BPaL regimen, for MDR/RR-TB patients resistant to fluoroquinolones (5/6 83% -Yes)
Belarus 	Yes	Yes
Georgia 	Yes	Yes
Kyrgyz Republic 	Yes	Yes
Republic of Moldova 	Yes	No
Ukraine 	Yes	Yes
Uzbekistan 	Yes	Yes

Results: National Treatment Guidelines and Policy (cont'd)

World Health Organization
REGIONAL OFFICE FOR Europe

Country	Mechanism of direct adoption of the WHO policy documents exists (3/6 33% -Yes)	The updated nat. guidelines will include the mSTR regimen (4/6 67% -Yes)	The updated guidelines include the longer or salvage regimen in case of BPaL(M) failure or ineligibility? (6/6 100% -Yes)
Belarus 	No	Yes	Yes
Georgia 	No	Yes	Yes
Kyrgyz Republic 	No	No	Yes
Republic of Moldova 	No	No	Yes
Ukraine 	Yes	Yes	Yes
Uzbekistan 	Yes	Yes	Yes

Results: Implementation coverage of the treatment policy and service delivery

World Health Organization
REGIONAL OFFICE FOR Europe

Country	% enrolled on standard 9-month, all-oral, bedaquiline-containing regimen in 2021 (Average 9%)	% enrolled on mSTR regimen in 2021 under regional or country cohorts OR (Average 32%)	% enrolled on fully oral longer 18-20 month regimen in 2021 (Average 43%)
Belarus 	0	65%	35%
Georgia 	0	61%	25%
Kyrgyz Republic 	8%	9%	79%
Republic of Moldova 	40%	22%	5%
Ukraine 	6%	27%	29%
Uzbekistan 	2%	10%	86%

Results: Implementation coverage of the treatment policy and service delivery (2)

World Health Organization
REGIONAL OFFICE FOR Europe

Country	% enrolled on 6-9 months BPaL regimen in 2021 within operational research (Average 4%)	% enrolled on a salvage regimen in 2021 (Average 9%) Salvage regimen is a type of treatment given to a patient after failure or non-response to other above mentioned therapies	plan to start or continue the implementation (enrollment of patients) of the BPaL OR in 2023 and beyond (5/6 83% - Yes)
Belarus	3%	6%	Yes
Georgia	6%	7%	Yes
Kyrgyz Republic	3%	0%	Yes
Republic of Moldova	0%	11%	No
Ukraine	7%	32%	Yes
Uzbekistan	3%	0%	Yes

Results: Implementation coverage of the treatment policy and service delivery (3)

World Health Organization
REGIONAL OFFICE FOR Europe

Country	% of registered countrywide DR-TB patients hospitalized for treatment in 2021 (Average 86%)	Average hospitalization length of stay in days for DR-TB patients in 2021 (Average 83 days)	VST coverage of TB patients in percentages as in 2021 (Average 35%)
Belarus 	100%	128	49%
Georgia 	80%	28	100%
Kyrgyz Republic 	NA	73	0%
Republic of Moldova 	87%	88	13%
Ukraine 	77%	100	40%
Uzbekistan 	NA	NA	5%

Results: Implementation coverage of the treatment policy and service delivery (4)

World Health Organization
REGIONAL OFFICE FOR Europe

Country	aDSM framework implemented with baseline and regular safety monitoring and established safety recording and reporting system (6/6 100% - Yes)	7 days / week DOT possible for MDR/RR-TB patients countrywide at outpatient level (5/6 83% - Yes)
Belarus 	Yes	Yes
Georgia 	Yes	Yes
Kyrgyz Republic 	Yes	Yes
Republic of Moldova 	Yes	No
Ukraine 	Yes	Yes
Uzbekistan 	Yes	Yes

Results: Drug supply and management

World Health Organization
REGIONAL OFFICE FOR Europe

BPaLM drugs registration Status, availability and funding

- Bedaquiline and Linezolid are registered in 50% of countries (Belarus, Kyrgyz, Ukraine – yes)
- Moxifloxacin registered in 100%
- Pretomanid registered in 5/6 (except Moldova)
- All regimen drugs are available in 100% of countries, except for pretomanid in Moldova
- Funding source of regimen drugs: 4/6 both TGF and Government, 2/6 only GF (MSF involved in Belarus)
- Allocated funding is sufficient for 100% of the countries

Results: Drug supply and management (2)

- 5/6 countries plan countywide implementation of the BPaL(M), Uzbekistan in pilots
- Belarus, Uzbekistan report they already started enrolment on the BPaLM regimen, Georgia, Kyrgyz Republic, Moldova, Ukraine plan after official recommendations or in 2nd quarter of 2023
- In total 1408 patients are expected to be enrolled on the regimen during the first year of implementation within the 6 countries
- 5/6 countries have a mechanism for importing unregistered pharmaceutical products into the country (question not applicable for Kyrgyz Republic as all BPaLM drugs are registered)
- 100% (6/6) countries conducted an assessment of the drug need taking into account the introduction of the new BPaLM regimen, and based on the assessment:

Results: Laboratory Diagnostics

- Access to rapid molecular WRD (Xpert MTB-RIF ultra) ensured for all presumptive cases countrywide for 100% of cases in these countries
- >90% coverage of access to rapid molecular second line DST (Xpert XDR or HAIN MTBDRsl)
- 4/6 report National TB Diagnosis guidelines are updated in line with the 2021 WHO guideline on rapid diagnostics (module 3)
- Technical assistance is needed to update the patient triage and laboratory algorithm for BPaLM implementation in 4/6 countries
- 100% of countries have access to phenotypic DST (recommended by WHO) to the BPaLM regimen drugs plus delamanid
- 2/6 countries report there are not enough funding allocated for procurement of the laboratory reagents/equipments in state budget or the Global Fund Grant (Kyrgyz Republic and Uzbekistan)
- 3/6 countries (Bel, Geo, Krg) report they have equipment for the Whole Genome Sequencing (WGS)

In Summary

- National treatment guidelines will include recommendations on 6 months BPaLM regimen as a regimen of choice for MDR/RR-TB patients in all 6 countries in 2023;
- 4 countries will preserve mSTR for certain target groups
- On average in 2021 coverage of MDR/RR-TB patients with: shorter regimens was 45%, fully oral longer regimens 42%, salvage regimen 11% (2% unknown)
- Quite high percentage of hospitalization (86% of MDR/RR-TB patients) and long hospitalizations (average 83 days, min-max range 28-128 days)
- Low coverage with Video supported treatment, VST (Average 35%, min-max range 0%-100%)
- Well implemented aDSM framework and good supply of drugs
- Access to rapid molecular WRD to 1st and 2nd line drugs ensured for >90% of cases
- Challenges with adequate funding for procurement of the laboratory reagents/equipments for some countries

Acknowledgements

Special thanks to WHO Euro region **mSTR task force and BPaLM subgroup** members and **Stop TB/GDF** regional technical advisors for their inputs to the questionnaire

Many thanks to the **NTPs of the countries** for completing the questionnaire and valuable input!

Thank you!

World Health Organization
REGIONAL OFFICE FOR Europe

WHO Regional Office for Europe

UN City
Marmorvej 51
Copenhagen Ø
Denmark

WHO_Europe

facebook.com/WHOEurope

instagram.com/whoeurope

youtube.com/user/whoeuro

World Health Organization
REGIONAL OFFICE FOR Europe

Weltgesundheitsorganisation
REGIONALBÜRO FÜR Europa

Organisation mondiale de la Santé
BUREAU RÉGIONAL DE L' Europe

Всемирная организация здравоохранения
Европейское региональное бюро