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REGIONAL OFFICE FOR **Europe**

Regional Green Light Committee for the WHO European
Region face-to-face meeting and workshop with high
drug-resistant tuberculosis burden countries:
programmatic aspects of the implementation of new
tuberculosis drugs and regimens

Copenhagen, Denmark, 18–20 June 2018

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Abstract

A face-to-face meeting of the regional Green Light Committee for the WHO European Region (rGLC/Europe) was held in Copenhagen, Denmark on 18 June 2018. The rGLC/Europe meeting was followed by a workshop on 19–20 June on the “Programmatic aspects of the implementation of new tuberculosis drugs and regimens” co-organized with the Laboratories, Diagnostics and Drug-resistance team of the Global TB Programme (GTB). The objective of the rGLC/Europe meeting and following workshop were to discuss uptake of current WHO policies on treatment and care for multidrug-resistant tuberculosis (MDR-TB) through the lens of early experience with the introduction of new drugs and shorter regimens in implementing countries, including the experience of the endTB project in European Region countries. The meeting also aimed to assist countries in the process of revising their national MDR-TB treatment policies based on current WHO recommendations and programmatic experience. Workshop participants included members of the rGLC/Europe; representatives from the Stop TB Partnership, the Global Drug Facility, the United States Agency for International Development (USAID) and Unitaid; country representatives from Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, the Republic of Moldova, Romania, Tajikistan, Ukraine, and Uzbekistan; staff from the WHO Headquarters Global TB Programme and from the Joint Tuberculosis, HIV and Viral Hepatitis Programme of the WHO Regional Office for Europe. Based on the discussions of the three-day meeting, a set of recommendations were proposed for WHO and partners.

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Abbreviations

ADR	adverse drug reaction
aDSM	active TB drug safety monitoring and management
BDQ	bedaquiline
CSO	civil society organization
DLM	delamanid
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
EECA	eastern Europe and central Asia
ELI	European Tuberculosis Laboratory Initiative
ERI-TB	European Tuberculosis Research Initiative
GDF	Global Drug Facility
GDI	Global Drug-resistant TB Initiative
HIV	human immunodeficiency virus
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
MDR/XDR-TB	multidrug and extensively drug-resistant tuberculosis
MXF	moxifloxacin
MoH	Ministry of Health
MSF	Médecins Sans Frontières
NAP	National Action Plan to Combat TB (USA)
NTP	National Tuberculosis Programme
PIH	Partners in Health
PZA	pyrazinamide
QTcF	QT interval Fredericia corrected for heart rate
rGLC/Europe	regional Green Light Committee for the WHO European Region
RR-TB	rifampicin-resistant tuberculosis
SAE	serious adverse event
STR	shortened treatment course regimen
SLD	second-line drug
TB	tuberculosis
TB-REP	TB Regional EECA Project
UNHLM	United Nations High Level Meeting
USAID	United States Agency for International Development
VOT	video observed therapy
XDR-TB	extensively drug-resistant tuberculosis

Introduction

The regional Green Light Committee for the WHO European Region (rGLC/Europe) was established in 2010 in response to the high burden of multidrug-resistant tuberculosis (MDR-TB) in the Region. It serves as the advisory body of WHO on the development and implementation of practical approaches for the prevention and management of multidrug and extensively drug-resistant tuberculosis (MDR/XDR-TB). It also provides technical assistance to the Member States of the WHO European Region and key partners in developing, updating and implementing a programmatic approach to the management of drug-resistant tuberculosis (DR-TB). The rGLC/Europe is hosted by the WHO Regional Office for Europe.

A rGLC/Europe meeting was held on 18 June 2018 in Copenhagen, Denmark. The meeting consisted of a one-day face-to-face meeting of the rGLC/Europe and was followed by a two-day workshop on the “Programmatic aspects of the implementation of new tuberculosis drugs and regimens”, on 19 – 20 June 2018 with additional participants from countries, donor organizations and WHO network. The objectives of the workshop were: to discuss uptake of current WHO policies on MDR-TB treatment and care through the lens of early experience with the introduction of new TB drugs for DR-TB and shorter regimens for MDR-TB in implementing countries, including the experience of the endTB project in countries in the European Region, and to assist the countries in the process of revising their national MDR-TB treatment policies based on WHO recommendations and programmatic experience.

The rGLC/Europe meeting was opened by Dr Masoud Dara (WHO Regional Office for Europe, Coordinator, Communicable Diseases; and Programme Manager, Joint Tuberculosis, HIV and Viral Hepatitis Programme). Dr Dara welcomed the participants and colleagues joining the meeting via WebEx. He reminded participants that although improvements in MDR/XDR-TB treatment outcomes have been achieved, the Region needs to progress faster. Dr Dara highlighted the importance of the United Nations High Level Meeting (UNHLM) on tuberculosis (TB) taking place on 26 September 2018 at United Nations Headquarters in New York, which is the first ever high-level meeting on TB. It is critical that the high burden of MDR-TB in the European Region is addressed in the outcome document. Dr Andrei Mariandyshev (rGLC/Europe chair) thanked participants and noted that due to new diagnostic tools and drugs, the Region has a great opportunity to end TB. Dr Ogtay Gozalov (Medical Officer, Joint Tuberculosis, HIV and Viral Hepatitis Programme) was the responsible officer for the meeting.

The rGLC/Europe meeting and the workshop were live streamed and recorded via WebEx for colleagues to participate remotely. PowerPoint presentations and meeting recordings are available on request to Dr Ogtay Gozalov (gozalovo@who.int). No conflicts of interest were declared. The agenda was reviewed and accepted (Annex 2). All participants submitted their consent to being photographed.

The rGLC/Europe discussed the election of a new rGLC chair and vice chair. Dr Dara expressed deep gratitude to previous chair Dr Andrei Mariandyshev and vice chair Dr Andrei Mosneaga for their commitment and the excellent job done in their capacity and role within rGLC/Europe. The rGLC/Europe proposed the election of Dr Alena Skrahina as the new chair and Dr Askar Yedilbayev as the new vice chair. No objections were made and Dr Skrahina and Dr Yedilbayev were welcomed to their new positions.

The points raised during the ensuing discussion sessions are summarized in this report.

rGLC/Europe face-to-face meeting, 18 June 2018

Follow-up/updates on previous meeting recommendations and updates from the rGLC/Europe Secretariat

Dr Ogtay Gozalov

Dr Gozalov reviewed the recommendations from the 2017 rGLC/Europe meeting. The majority of the recommendations have been adopted or are in progress. The status of the recommendations from 2017 is outlined below.

Dr Gozalov reviewed the purpose and reporting procedures for rGLC missions. Missions are no longer for monitoring purposes. They are intended to provide technical recommendations and support countries. Mission reports should be sent to the rGLC within four weeks of mission completion as editing, translation and peer review takes four weeks. The memorandum of understanding with countries outlines that reports are to be presented to the country within 60 days of completion of the mission. The names of technical editors, language editors and those responsible for report clearance have been added to the report. Finalized reports are publicly available. Prior to clearance and submission to the mission country, the report is sent to the Global Fund to Fight AIDS, Tuberculosis and Malaria portfolio managers for input and approval.

Table 1. Status of the 2017 rGLC face-to-face meeting and workshop recommendations

	Recommendation	Status
1	Use the momentum to advocate for increased political commitment to TB control during the ministerial meeting in 2017. WHO Regional Office: prepare bullet points for the Regional Director to use in meetings with ministers attending the conference.	Done/ongoing The bullet points were used at the ministerial conference in Moscow in November 2017.
2	Continue the work of the Joint Tuberculosis, HIV and Viral Hepatitis Programme with the Division of Health Systems and Public Health (DHS&PH) to ensure TB programmes are part of the ongoing health systems reform in countries. The TB Regional EECA Project (TB-REP) can facilitate these processes and share good practice among countries. Share reports with the DHS&PH and invite them to follow-up calls on implementation of the rGLC/Europe recommendations.	Done/ongoing Colleagues from the WHO DHS&PH have been involved in incorporating the work into all of the countries in the Region.
3	The rGLC/Europe Secretariat in collaboration with WHO country representatives and country officers: communicate with the ministry of health (MoH) and partners in countries ahead of rGLC missions and share the terms of reference to ensure successful rGLC and other technical assistance.	Done/ongoing Mission members receive information ahead of the mission.
4	Discuss with national tuberculosis programme (NTP) managers the possible ways in which the MoH could be more closely involved in the implementation of the national strategic plans, national TB action plans, plans for the introduction of rapid diagnostics and people-centred care.	Done/ongoing Engagement of MoH are discussed during missions.
5	Consider searching for additional funding to enlarge the pool of rGLC consultants.	Done/ongoing Work is ongoing to include junior

	consultants on missions for training purposes.
6	Consider searching for additional funding to enlarge the rGLC/Europe Secretariat.
7	Facilitate the revision of the format of the report and supporting documents of the rGLC technical assistance missions, including enrolment targets, actual needs for new TB drugs and diagnostics.
8	Agree on more focused terms of reference with NTPs and the MoH, prior to the rGLC mission, to define the technical assistance needs accordingly; differentiate between monitoring and technical assistance missions. Organize the post-mission follow-up phone calls with the NTP and partners to update on progress and plan ahead.
9	Encourage face-to-face discussions with key European Region governments and agencies to encourage TB-specific funding in the Region.
10	Encourage countries and provide technical assistance on updating the national action plans and advise on substantial increases in government funding.
11	Pursue financial gap analysis during the financial sustainability related missions. Ask the MoH about the financial gaps for TB in the countries. Invite the Global Fund to a workshop on financial analysis.
12	Add a new format to regular WHO recording and reporting, with a breakdown of the number of cases per treatment regimen (or at least per medicine) during the particular time period (preferably broken down per month or quarter). Discuss the format of the information needed from the country with the Global Drug Facility (GDF).

consultants on missions for training purposes.

Not complete

Funding to increase staff has not yet been allocated. Work is continuing in this regard.

Done/ongoing

The revised mission report has been pilot tested with success. Use of the new format is challenging; however, it is more country and user friendly and becomes easier to use after each mission.

Done/ongoing

Work is ongoing to ensure that missions have a technical purpose, rather than monitoring.

Partially done

Meetings are held in person and are streamed and recorded via WebEx to share knowledge and information with all interested colleagues.

Done/ongoing

Work is ongoing to ensure sustainability after the withdrawal of donor organizations. One country in the region plans to procure drugs using national funds next year.

Ongoing

This is ongoing via Regional Platform. Four countries have conducted financial gap analysis and two more are in the process. The results will be shared in Tbilisi, September – October 2018.

Done/ongoing

Work is ongoing to include a breakdown of patient numbers; however, countries continue to criticize the excessive number of reports and remain confused on the reporting formats for treatment outcomes of patients on new drugs/regimens.

Update from the European Tuberculosis Laboratory Initiative (ELI)

Dr Soudeh Ehsani

ELI was initiated six years ago by the WHO Regional Office for Europe in close collaboration with the Global Laboratory Initiative (GLI), WHO headquarters and the Stop TB Partnership. The current core group members represent academia, WHO, supranational and national TB reference laboratories, and various other TB laboratory experts. The members come from Armenia, Azerbaijan, Belarus, Georgia, Germany, Kyrgyzstan, the Russian Federation, Sweden, Tajikistan and the United Kingdom. Following WHO recommendations on the use of rapid molecular TB and MDR-TB diagnostic methodologies, ELI developed a regional diagnostic algorithm, technical documents for strengthening laboratory services and a training toolkit for the use of line probe assays for second-line anti-TB drugs (SL-LPA). During these trainings more than 100 specialists, including those from all nine high MDR-TB burden countries, have been trained in the use of the diagnostic algorithm.

A toolkit with six modules has been developed. Following the algorithm training, participants were trained on SL-LPA at the WHO Collaborating Centre for Research and Training in Management of Multidrug-Resistant Tuberculosis, Riga, Latvia. Additional country trainings have been provided in Belarus, Kyrgyzstan and Uzbekistan, with excellent participant satisfaction survey results. Through the use of pre- and post-training tests the specialists' knowledge on SL-LPA use showed an improvement from 43–52% in the pre-training test to 82–96% in the post-training test. The toolkit is being finalized for autonomous use as an online training toolkit. Other ELI activities include specialist trainings for laboratory safety, such as the maintenance of biosafety cabinets and ventilation systems. ELI works in collaboration with NTPs, national reference laboratories, the rGLC/Europe and other relevant organizations (European Centre for Disease Prevention and Control, GLI, Better Labs for Better Health and others).

More information about ELI can be found on the ELI web page.¹

Summary of questions and comments

- The SL-LPA toolkit is field oriented and is being translated into Russian.
- A mentoring programme is in place for engineers who have already been trained.
- TB laboratory maintenance and biosafety trainings are extremely important, however, there is a question of funding for these activities. Two engineers have been trained so far per trained country (a total of six countries, with an additional five being added to the list in 2018 and 2019) and further funding and use of the engineers is dependent upon national funding mechanisms. WHO, in close collaboration with NTPs, will work on finding sustainable funding mechanisms to cover the costs through national funding.
- Europe has no standard national mechanisms for the certification of biosafety cabinets, as in the United States. However, cabinets must be certified according to the standards on which the cabinet was initially certified by the manufacturer. As an example, a manufacturer based in the United States can produce certified cabinets based on various standards.
- International Organization for Standardization (ISO) accreditation of laboratories is of high importance; however, countries should bear in mind that accreditation is a long process, which can last for several years. All capacity-building activities supported through ELI and the Regional Office (e.g. trainings, technical documents such as the algorithms, the maintenance plan, etc.) are important for ISO 15189 accreditation.

¹ About the European Tuberculosis Laboratory Initiative (ELI). In: WHO Regional Office for Europe [website]. Copenhagen: WHO Regional Office for Europe; 2018 (<http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/areas-of-work/laboratory-diagnosis/about-the-european-tuberculosis-laboratory-initiative-eli>, accessed 30 July 2018).

Update from the European Tuberculosis Research Initiative – a catalyser of innovative TB care

Dr Andrei Dadu

Dr Dadu reminded participants that the Region has one of the fastest declining rates of TB incidence; however, the rise of MDR-TB and HIV threaten the vision to End TB in the Region. Therefore, it is important to apply innovative methods. The European Tuberculosis Research Initiative (ERI-TB) was launched on 15 October 2016 with the aim of identifying regional TB research priorities and facilitating country capacity-building on implementing this research agenda. A regional agenda to foster research and innovation for new tools and to optimize innovation implementation was jointly developed by the core group members of ERI-TB and public consultations were held, facilitated by its secretariat at the WHO Regional Office. Country-level ERI-TB research focuses on ongoing transmission of MDR/XDR-TB, acquired resistance to second-line drugs (SLDs), HIV/TB coinfection, strengthening national TB programmes, TB and comorbidities, the impact of migration and other determinants on the TB epidemic in the Region, and TB in prisons. The three themes determined by the research are epidemiological research, innovation and fundamental research, and operational research. The results were presented in a manuscript, which has been accepted by the International Journal of Tuberculosis and Lung Disease. Dr Dadu also presented the ERI-TB workshops stream for 2018–2019, which aims to develop countries research capacity in implementing the European Region TB research agenda. Dr Dadu acknowledged that the United States Agency for International Development (USAID) continues support research capacity development in the European Region within the framework of the WHO regional partnership project to End TB in East Europe.

More information on ERI-TB can be found on the ERI-TB web page.²

Updates on the TB-REP regional project

Dr Martin van den Boom

Dr van den Boom reminded participants that TB is a social disease. The MDR-TB community is making progress but has not yet reached the target of 75% treatment success, set out in the Tuberculosis Action Plan for the WHO European Region 2016–2020. TB-REP conducted an analysis on the barriers to treatment success. The areas identified as needing improvement are governance, service delivery, health financing, pharmaceuticals and human resources. The goal of the project is to decrease the burden of TB, increase political commitment and increase implementation of TB programming.

The regional action plan is based on the principle of people centeredness, not patient centeredness. A people-centred model of care has been developed in collaboration with partners and member countries. The project results have been encouraging: with 8 out of 11 countries adopting priorities for TB care through a people-centred approach; an increase in the share of TB in national health budgets; a decrease in hospitalization rates from 75% in 2015 to 56% in 2017; and a decreased length of hospital stays from 158 days to 109 days on average. Other essential elements of the project are advocacy at the high level, facilitating people-centred care, developing in-country strategies for civil society organizations (CSOs), and increasing intersectoral collaboration at the country level.

Summary of questions and comments

- There is a question of sufficient access to key decision-makers, in order to increase the allocation for TB in the national budget and render budget allocation and spending more efficient and sustainable. A high-level letter

² The European Tuberculosis Research Initiative (ERI-TB). In: WHO Regional Office for Europe [website]. Copenhagen: WHO Regional Office for Europe; 2018 (<http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/areas-of-work/the-european-tuberculosis-research-initiative-eri-tb>, accessed 30 July 2018).

was signed by the WHO Regional Office, the Global Fund, and the Stop TB Partnership to address these issues, and to obtain high-level national political commitment for the project. This year a high-level ministerial TB-REP breakfast will be held in Rome, Italy, as an official side event of the Regional Committee for European WHO Member States (MS). High-level involvement needs to be coupled with CSO engagement to meaningfully support patients.

- A higher level of commitment for funding for universal health coverage is needed. The UNHLM on TB is an important opportunity to address this issue. TB-REP is highly involved the development of messages to be delivered to country representations attending the meeting. In preparation for the UNHLM, a regional TB-REP alliance for global health has been formed. The alliance is informing CSOs in the region about the topic and will discuss the approaches that civil society can use to prepare for the UNHLM. Long-lasting and effective translation of political commitment into action and tangible improvements of TB prevention and care, including beneficial health system reforms and transformations, is also a topic which is operationalized in order to prepare MS for implementation of an accountability framework related to the UNHLM on TB, confirmed for 26 September 2018
- The TB-REP reports are approved by countries and, provided they agree, may be publicly available following finalization.
- A follow-up project, a TB-REP 2, has been developed by a similar consortium of players, including the WHO Regional Office, and submitted for review and approval of the Global Fund on 30 April 2018. At the time of the meeting, the outcome of the submission was unknown. The project aims to consolidate and further expand progress made under the current TB-REP project, which is in its final year of implementation.

Panel discussion 1. Improvement of treatment success of M/XDR-TB and the role of the rGLC/Europe in that

Chair: Dr Alena Skrahina

Panel: Dr Andrei Mosneaga, Dr Kai Blöndal, Dr Askar Yedilbayev

Updated guidelines for the treatment of DR-TB. WHO is planning the update of the guidelines for treatment of DR-TB, which will likely become available by the end of 2018, following consultations in Geneva in July 2018. The guidelines revision will consider more evidence generated from several international projects and countries' experience on the use of new TB drugs, bedaquiline and delamanid, for treatment of MDR/XDR-TB. It is important to update guidelines and recommendations, however, barriers to implementation of recommendations must be addressed, including access to diagnosis and treatment.

Retreat of the Global Fund. The retreat of The Global Fund is a major challenge in the Region, particularly as drug resistance in the European Region is high. Countries and NTPs must work on a smooth transition from the Global Fund to national funding. Participants were reminded that if countries do not provide good quality and timely reports to the Global Fund, the country risks losing all of its funding from the organization.

Shorter treatment regimens. There is general optimism that shorter treatment regimens will support improved treatment outcomes; however, barriers to proper implementation remain. Barriers include a high level of drug resistance in the Region and the limited capacity of laboratory services to rapidly diagnose resistance to the drugs used in the shorter regimen, especially to SLDs. The rGLC is looking forward to the release of the revised version of the WHO guidelines, where updated recommendations on the use of the shorter regimen for MDR-TB may be included.

Role of the rGLC/Europe. The rGLC/Europe are not consultants, but partners to countries implementing MDR/XDR-TB programming. One of the primary regional priorities is the improvement of treatment outcomes.

To provide adequate support, the rGLC/Europe depends on countries to advise the rGLC on their specific country needs. The rGLC cannot go beyond the authority of ministries of health; therefore, it is critical to address issues of health system strengthening. National councils of physicians can be strong allies in this regard. The main role of the rGLC/Europe is to improve overall health system organization, engage with primary health care, and influence legislation. In addition, the rGLC provides technical assistance during rGLC missions, provides recommendations and general guidance on programme and medical management of DR-TB, and identifies the need for additional external technical assistance to address the gaps. Moreover, the rGLC serves as an advisory board to the WHO Regional Office for Europe on issues of DR-TB regional policy.

rGLC missions. Missions are not for monitoring purposes but should focus on technical support. In larger countries it can be difficult to collect sufficient data on a country in the five days allocated for missions. Therefore, it is important for NTPs to inform the rGLC in advance of the needs of the mission, including the problematic areas and length of time needed for the mission.

Mission reports. NTP managers must use the updated mission reporting format. The report allows for NTPs to view different perspectives on their programmes. It is a challenge that NTP managers do not always have enough time to fill out the mission reports, therefore, they must have sufficient human resources to support the good-quality completion of reports. There is concern that few country representatives read or internalize the recommendations of the annual report. The Tajikistan NTP demonstrated best practice by writing a response on the status of implementation of WHO recommendations. It is challenging for a single consultant to be specialized in the many areas that need technical support, therefore, missions should have a focus area/theme, so the correct consultant can be assigned to the task.

Treatment outcomes. On average, MDR-TB patient outcomes have improved; however, the Russian Federation (where the rGLC has no leverage) has a significant bulk of the MDR-TB patients in the Region, which impacts the average for the Region. Treatment outcomes are analysed in 3–5-year cycles, thus the outcomes of work completed this year may not be available for three years. Therefore, proxy indicators for outcomes should be considered, for example culture conversion, number of people defaulting, and/or deaths. Some causes of poor treatment outcomes are late diagnosis, poor quality laboratory tools and drugs, and a lack of people-centred care.

People-centred approach. The focus on people-centred approaches needs to be increased. Shorter term regimens are recommended to countries as having demonstrated a significant number of treatment successes; however, this Region has one of the highest rates of loss to follow-up, indicating that the current 20-month treatment regimens are not acceptable to patients, and thus, are not people centred. Shorter treatment regimens are potentially more acceptable to patients, as duration of therapy is decreased to 9–12 months. Introduction of patient-centred accompaniment models of care should be considered as another priority for the Region.

WHO European Region as a model and best practices for DR-TB. Other regions look to the European Region as a model for what is possible concerning the programmatic and medical use of new TB drugs and other best practices. The European Region should have the capacity to implement shorter and more individualized treatment regimens. Moreover, countries within the Region should observe best practices from others in the Region. For example, Kazakhstan has had the highest treatment success in the Region. Other countries should analyse how Kazakhstan's success can be scaled up in their countries.

Quality. Good diagnostic, treatment and drug quality are essential and should be the number one priority, especially as countries go through the transition from Global Fund to national funding. The quality of drugs used

after the shift to national funding is of particular concern as locally produced drugs may be prioritized, even if these drugs are not of high quality. Decision-makers should be engaged to ensure that procured drugs are of sufficiently high quality. One solution is to promote the WHO prequalification process with national governments.

Procurement. Procurement of MDR/XDR-TB drugs and diagnostic tools is challenging in many countries.

Panel discussion 2. Messages from the rGLC/Europe to the UNGA on TB

Chair: Dr Alena Skrahina

Panel: Dr Elmira Gurbanov, Dr Andrei Maryandyshev, Dr Liga Kuksa

UNHLM on TB, process. The first ever UNHLM on TB will take place on 26 September in New York. A draft resolution was discussed at the Seventy-first World Health Assembly in May 2018. All NTPs should promote the recommendations at the highest level for their missions attending the UNHLM on TB.

Draft recommendations. The recommendations are based on the End TB Strategy and focus on supporting, together with all relevant stakeholders, the implementation of the Moscow Declaration to End TB,³ as a direct contribution to the success of the UNHLM, in the following ways:

- ✓ develop actions to strengthen health systems towards achieving universal health coverage, including for TB prevention and care;
- ✓ urgently support high MDR-TB burden countries in their national emergency response;
- ✓ address MDR-TB as a major threat to public health security by supporting implementation of the Global Action Plan on Antimicrobial Resistance, including TB-specific actions in all countries;
- ✓ continue to provide strategic and technical leadership, assistance and advice to support Member States, as well as working with international institutions and all other relevant stakeholders, towards sufficient and sustainable financing;
- ✓ develop a global strategy for TB research and innovation, taking into consideration both ongoing and new efforts, and make further progress in enhancing cooperation and coordination in respect of TB research and development;
- ✓ continue to develop, in consultation with Member States, the draft multisectoral accountability framework, working in close collaboration with all relevant international, national and regional partners as recommended in the Moscow Declaration to End TB (2017), and to provide technical support to Member States and partners.

Key messages. The key messages must be high level, brief, specific, non-technical and designed for use by civil society and for advocacy. Advocates should argue that the allocation of resources for TB is an economic opportunity, as it is more cost-effective to address the issue of MDR-TB now, rather than later. It is recommended to focus on allocation of resources and use the experience of HIV advocacy for inspiration. See Box 1 for potential themes for key messages.

³ Moscow Declaration to End TB. Geneva: World Health Organization; 2017. (http://www.who.int/tb/features_archive/Online_Consultation_MinisterialConferenceDeclaration/en/, accessed 1 August 2018).

Box 1. Potential themes for key messages for the UNHLM on TB

- missed cases;
- stigma;
- people-centred care;
- human resources for health;
- access to diagnostics and treatment;
- universal health coverage;
- drug quality assurance;
- procurement;
- financial resource allocation;
- legislative frameworks for MDR-TB;
- continuity of care;
- lowering the high cost of treatment;
- TB within the human rights based approach;
- development of multidisciplinary teams for people-centred care;
- prevention;
- accreditation of TB laboratories;
- access to quality laboratory equipment and properly trained staff;
- cost-effectiveness of interventions;
- TB in prisons.

Panel discussion 3. Partners and donors on the implementation of the European TB Action Plan

Chair: Dr Alena Skrahina

Panel: Dr Sevim Ahmedov, Dr Dumitru Laticevschi

TB status update. The goal of ending TB by 2025 is an ambitious target and may need to be recalibrated. In the European Region the main challenge is DR-TB. Globally, only 1 in 10 MDR-TB cases is being treated and the economic cost is substantial (US\$ 17 trillion lost in economic growth and productivity).

Update on the USAID bedaquiline donation programme. The agreement with the manufacturer to provide bedaquiline (BDQ) free of charge was extended until March 2019. Between April 2015 and March 2018, BDQ orders increased from 3895 to 23 859, which is close to the 30 000-order agreement with the manufacturer. Orders have been made in 69 countries. The GDF orders for delamanid (DLM) are not as high as for BDQ, as only 37 countries have ordered DLM.

National Action Plan to Combat TB. The goals of the National Action Plan (NAP) are: (1) to strengthen domestic (United States) capacity to combat MDR-TB; (2) to improve international capacity and collaboration to combat MDR-TB through improved access to high-quality, patient-centred diagnostic and treatment services and prevent MDR-TB transmission; and (3) to accelerate basic and applied research and development to combat MDR-TB. The NAP is in its third year and is active in 10 countries. No additional funding is available for NAP. The relevant 2020 target for the Region is to initiate appropriate treatment in 50% of patients with MDR-TB in 10 countries with the highest burdens of the disease. See Box 2 for the essential components of the NAP.

Box 2. MDR-TB NAP essential components

- timely – impact within 3–5 years
- strengthen existing efforts, collaborations and programmes
- increase options for preventing *M tuberculosis* infection, transmission and TB disease
- improve the diagnosis of TB – latent infection, drug-sensitive TB, MDR-TB and XDR-TB
- improve treatment options for individuals with drug-sensitive and MDR/XDR-TB
- increase the capacity of TB endemic countries to conduct biomedical and clinical research in TB.

USAID role. USAID typically provides technical support through the BDQ donation programme, webinars, workshops, missions, engagement with NTPs, support to Challenge TB, and support to TB advisors that have been embedded in NTPs. The work of MDR-TB advisors is not intended to duplicate the work of the rGLC, but to complement its activities. The USAID missions are designed as follow-up to rGLC missions.

Severe adverse events reporting. The majority of severe adverse event (SAE) reports are from endTB project sites and reflect an enhanced capacity for active TB drug safety monitoring and management (aDSM). More than 65 countries use BDQ and DLM under programmatic conditions, but only 30% have reported SAEs through the GDF, reflecting limited or no capacity for aDSM. aDSM is a critical component for the introduction of new drugs (BDQ/DLM) and shortened treatment course regimens (STR).

Primary challenges. Shorter regimen uptake is increasing but remains slow compared to needs. Clinical management needs further capacity-building. Many MDR-TB patients are on SLDs, however, only around 50% have drug susceptibility profiles. It is not acceptable to put patients on highly toxic regimens without strong drug susceptibility results. Partner coordination to ensure consistent recommendations from all organizations can be strengthened. Off-label use of BDQ should be reported through the same channels as adverse effects.

Summary of questions and comments

- **Role of drug susceptibility testing.** Quality is a critical component. The scale-up of new drug treatment is good, however, focus needs to be increased on how to align the rate of treatment scale-up with testing and adherence, so resistance to new drugs is not increased unnecessarily. Drug susceptibility testing (DST) and other laboratory/diagnostic issues should be at the forefront of discussions. No patient should be on a new drug treatment without being fully tested.
- **Advocacy at the UNHLM on TB.** The need for continued access to BDQ after the end of the donation programme in March 2019 could potentially be included in the key messages at the UNHLM on TB.
- **National financing.** Currently, no country has included BDQ in their Global Fund proposals, as no budget could accommodate BDQ orders. It is assumed that countries will order for all 2019 cases through the donation programme. The situation beyond 2020 is a cause for concern, as some countries cannot procure BDQ through the GDF, and in other countries the cost of procuring BDQ locally is extremely high.
- **Drug registration.** Where it has been possible, BDQ has already been registered (Turkmenistan, Ukraine, Uzbekistan). Some countries rejected BDQ registration due to lack of phase III trial results (Kazakhstan, Kyrgyzstan, Tajikistan). BDQ will most likely be registered in Georgia next year, and registration is pending in Belarus and the Republic of Moldova. Registration of DLM is slower compared to BDQ, due to the relatively limited market and the fact that the manufacturer should be in charge of registration.

Panel discussion 4. Development of recommendations to WHO and the rGLC/Europe

Chair: Dr Alena Skrahina

Panel: Dr Askar Yedilbayev, Dr Kai Blöndal, Dr Andrei Mosneaga

Missions. Missions are to be technical in nature and meet the needs of each individual country. They should be planned 3–4 months in advance and be by request of the country. At the end of each year, the rGLC sends an Excel sheet with preliminary mission dates for each country; however, for some countries it can be difficult to plan this far in advance. Typically, the rGLC makes one visit per year, as ministries of health often do not welcome higher mission frequency. Countries should request the technical areas of need and the secretariat will assign an appropriate consultant. The goal of the missions is not to put blame on countries, but to facilitate programme improvement using a systematic approach. This should be communicated to MoHs. Countries do not need to have regular missions but can also be supported by the rGLC in other ways, such as capacity-building exercises. If possible, missions should conclude with some sort of training. Meeting with the MoH is not necessary for each mission.

Mission reporting. The new report format is very useful. However, for some countries it is impossible to gather the requested data. The recommendation is to collect as much data as possible now, to have a good starting

point for future data analysis. There is a challenge for some countries in that the mission reports do not highlight the truth about the country situation because NTPs do not want to create friction with the MoH if the report is negative. It is unclear how to improve on this situation.

Procurement. If the needs for technical assistance are urgent, countries can contact the GDF.

Pharmacovigilance. This year a pharmacovigilance component is mandatory in countries that use Global Fund grants.

Capacity-building. Capacity-building should be done through mentorship and missions. Missions should include workshops or other capacity-building activities, as requested by the country.

Standard indicators. There was a request to develop a set of standard indicators for the Region to assess programmes and facilities, however, the rGLC does not want to implement indicators as part of missions. If countries have standard indicators, the missions will become monitoring in nature, which is not the goal.

Access to key stakeholders. Countries requested that the rGLC facilitate access to key government stakeholders to discuss the main challenges of TB control, however, it is difficult to do this as government officials often cancel or change plans at the last minute.

Data. TB information systems and data are generally poor. The information system's main purpose is to improve quality of care and facilitate the work of NTP managers. It can be time consuming to properly input data, however, it is critical to improve the quality of care.

Prequalification. Prequalification is an extensive process; however, it is valuable for countries in the long run. If they have urgent needs for technical assistance countries can contact the GDF.

Workshop on programmatic aspects of the implementation of new TB drugs and regimens for DR-TB treatment in the WHO European Region, 19–20 June 2018

Dr Masoud Dara welcomed new meeting participants. He repeated that 2018 is an important year for TB because of the UNHLM on TB. Dr Fuad Mirzayev thanked the organizers of the meeting, noting that the timing is critical for MDR-TB. The DR-TB community is on the verge of accepting new guidelines, so it is important to have discussions with implementing countries to ensure alignment between guidelines and implementation.

Session 1. Current policies and status of implementation, presentations and discussion ***WHO guidelines for management of DR-TB and patient care (Dr Ernesto Jaramillo)***

WHO is updating MDR-TB guidelines this year. A review was planned for 16-20 July and new guidelines are to be released in mid-October. WHO has used the GRADE system to develop new guidelines since 2007. GRADE is a methodology for conducting an independent and transparent assessment of available evidence. Organizations and individuals who have financial or intellectual conflicts of interest are excluded from participating in the development of the guidelines. In this update, and for the first time, WHO is making an open call for data contributors. Thus, the current data review for the update of the guidelines will include significant contributions from country-level programmatic data, including data produced under operational research conditions. Data from observational studies in West African countries, South Africa and Belarus and countries of the endTB project supported by Unitaaid, will be used in the policy update.

The updated guidelines will incorporate the results of the STREAM and DLM trials. The STREAM trial compared a shorter regimen with longer regimens. The preliminary results of the trial have failed to show non-inferiority of the shorter regimen. The trial reported higher mortality among people living with HIV in the intervention arm; however, the interpretation of this finding is problematic due to the fact that the design of this study was not powered to assess differences in this subpopulation.

Results for the DLM phase III trial do not show efficacy in terms of treatment outcomes. However, the potential efficacy of DLM cannot be ruled out either, due to the fact that the trial was not powered to assess efficacy. The trial results indicate that DLM has a favourable safety profile.

WHO released rapid advice on the implementation of current recommendations, in order to dispel confusion on the implications of the results of these two trials. In short, the current WHO recommendations were not affected,^{4,5}

A very important finding in these two trials is the 80% treatment success reported for their control arms (global treatment success reported in the last five years is around 50%). This outcome reflects the importance of a people-centred approach to treatment delivery. That is, careful selection of patients, delivery of treatment according to the needs of patients (with social support), and aDSM. It is crucial to incorporate aDSM into the routine practice of MDR-TB management, not only to promote patient safety but also to contribute with data for policy updates.

⁴ Position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results. Geneva: World Health Organization; 2018 (<http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/WHOPositionStatementShorterRegimensSTREAMStage1.pdf>, accessed 30 July 2018).

⁵ WHO position statement on the use of delamanid for multidrug-resistant tuberculosis. Geneva: World Health Organization; 2018 (<http://www.who.int/tb/publications/2018/WHOPositionStatementDelamanidUse.pdf?ua=1>, accessed 30 July 2018).

BDQ is being authorized by regulatory authorities and recommended by WHO for use for only six months, in view of the lack of data on safety and effectiveness for longer use. WHO does not have a negative recommendation for the use of BDQ past six months; however, it cannot recommend it unless there is evidence suitable for a GRADE assessment. Therefore, patients and clinicians must evaluate each case and make a decision about off-label use beyond six months. WHO released a best practice statement to guide NTPs, clinicians and patients in the decision-making that may result in off-label use of BDQ or DLM.⁶

Unitaid: continued commitment to improving cure rates for people affected by MDR-TB (Ms Ekaterina Rykovanova)

One of the primary goals of Unitaid is to increase the amount of evidence for WHO. Unitaid provides partners with short-term grants to achieve maximum impact. The strategic objective is to maximize effectiveness of the global health response by catalysing equitable access to better health products. Unitaid works in three areas: innovation, access and scale. A call for proposals was made on 1 May and is open until 29 June for innovative projects to fight TB and DR-TB that can be quickly implemented. The proposals will be reviewed by early September for implementation to begin in early 2019.

The Unitaid-funded endTB project is being implemented in 17 countries across the globe, including 5 from the WHO European Region, from 1 April 2015 to 31 March 2019. At the very beginning, some countries were cautious about widely using the new drugs for several reasons, such as drug registration, regulations on importation, and lack of evidence on the use and drug costs. Current challenges for the use of new TB drugs are similar, but include increased demand, high costs of the drugs (e.g. DLM, the price of BDQ for eastern European countries after the end of the USAID-Janssen Bedaquiline Donation Program) and sustainability of access at country level.

Summary of questions and comments

- Coverage with DST, especially to SLDs, is not sufficient, and laboratories are not properly supported in countries that run MDR-TB programmes.
- Last year, only one proposal was approved due to the length, complexity and cost of the other proposals. This year the request for proposals is focused on:
 - improved access to DST, specifically using targeted gene sequencing platforms for clinical decision-making (e.g. replacing phenotypic DST), in low- and lower-middle-income countries;
 - targeted interventions to boost uptake of better MDR-TB regimens of commercially available drugs, subject to WHO guidance;
 - improved TB treatment outcomes through targeted innovative approaches to support adherence that can be implemented within the next two years.
- Supranational laboratories play a critical role in supporting their linked National TB Reference Laboratories.. Having testing for new medicines done at supranational laboratories is a first step, yet, support should be available to assist countries to set up national reference laboratories in settings where new drugs are used.

Update on the endTB project (global and regional) – Expanding new drug markets for TB (Dr KJ Seung, presented by Dr Askar Yedilbayev)

⁶ WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization; 2018 (<http://apps.who.int/iris/bitstream/handle/10665/258941/WHO-HTM-TB-2017.20-eng.pdf?sequence=1>, accessed 30 July 2018).

MDR-TB requires a highly complex treatment with up to two years of multiple drugs. Globally, in 2012, only 17% of MDR-TB patients received effective therapy and 79% of people living with MDR-TB never received an accurate diagnosis. The situation remains mostly unchanged since 2012. The gap between need and access is large. The endTB project is increasing the evidence base on the effectiveness and safety of the new TB drugs in order to expand markets for new TB drugs. The project will contribute to the upcoming revision of the WHO guidelines on DR-TB in July 2018.

The endTB observational study looks at safety and efficacy of new TB drugs to resolve questions on: the routine use of the drugs; combination use of BDQ and DLM; off-label use; use of the new drugs in patients with comorbid conditions like hepatitis C, diabetes and HIV; knowledge about clofazimine and linezolid; and subpopulation outcomes (children, pregnant women). Public resources include the open-source EMR and *endTB Clinical and programmatic guide for patient management with new TB drugs*.⁷ See Box 3 for details on the cohort and results of the observational study.

Another separate activity of the endTB project is a clinical trial, which is focused on identifying a regimen for MDR-TB which is short, effective and contains no injectable agent. The endTB clinical trial is a multicountry randomized control trial, implemented in 6 countries, 3 of which are in the WHO European Region. It has no restrictions on HIV and success would consolidate the market around priority drugs.

Box 3. endTB observational study cohort and interim results

Cohort

- 17 countries with more than 1800 patients enrolled as of November 2017, the projection is 2650 by October 2018;
- 1302 on BDQ, 749 on DLM, 182 on combination BDQ and DLM.

Results (interim)

- over 80% six-month culture conversion rate in patients with MDR-TB and XDR-TB enrolled between 1 April 2015 and 30 September 2016;
- 291/356 (82%) of all MDR-TB (including XDR-TB) patients had culture conversion at six months;
- 129/161 (80%) of XDR-TB patients had culture conversion at six months.

Summary of questions and comments

An example was given of a patient from Kazakhstan who had been suffering from TB for 18 years and developed XDR-TB. The patient was enrolled into the endTB project and started therapy with a BDQ-containing regimen. Culture conversion was achieved after 1 month of therapy. The patient underwent a pneumonectomy and completed treatment after 20 months, and was declared as “cured”. The patient achieved consistent culture conversion with 18 consecutive cultures. The case was presented to the national council of physicians, which recommended that the treatment stop as it had been successful.

Session 2. Status of introduction of Short treatment regimens and steps required to scale it up.

Status, potential scale-up and barriers to implementation of the shorter MDR-TB regimen in 18 high priority countries of the WHO European Region (Dr Elmira Gurbanova, Dr Liga Kuksa, Dr Nestani Tukvadze)

⁷ endTB clinical and programmatic guide for patient management with new TB drugs. Version 4.0. endTB Consortium; 2018 (<http://www.endtb.org/sites/default/files/2018-02/Guide%20for%20New%20TB%20Drugs%20Version%204.0%20final.pdf>, accessed 30 July 2018).

The study presented was a retrospective analysis in 18 high-priority countries to investigate how many patients could hypothetically be eligible for shortened chemotherapy regimens. Not all countries in the eastern Europe and central Asia (EECA) region use shortened regimens. In 2018, the STR was introduced in Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Tajikistan and Ukraine. Some countries failed to provide data on the status of STR introduction (e.g. Bulgaria, the Russian Federation, Turkey, Turkmenistan and Uzbekistan). About 53% of new pulmonary rifampicin-resistant TB (RR-TB) patients with available results for DST to SLDs in the region could be eligible for STR. It should be possible to increase the number of patients on STR, if countries can improve implementation of diagnostic algorithms utilizing rapid molecular TB tests as per WHO ELI recommendations. Although almost all countries adopted the WHO ELI recommended algorithm at the national diagnostics protocols, rapid tests are not always available. In EECA countries, rapid tests are mainly procured with Global Fund support; hence, the decrease in Global Fund funding in these countries planned for the forthcoming years may further decrease availability of the rapid TB tests. More than 90% of patients in the region have *Mycobacterium tuberculosis* (MTB) with *katG* mutations responsible for resistance to high-dose isoniazid. There is considerable room for improvement in TB medicines registration and implementation of aDSM activities. Another finding of the study is that almost all countries, except for Belarus, are using modified STR. It is important to follow internationally recommended guidelines for drafting study protocols, ethical clearance, informed consent, etc. to ensure quality, comparability and visibility of study results.

Summary of questions and comments

- The evidence on the standard short course regimen outcomes is certain only if strict selection criteria are duly followed; therefore, countries should take precautions and follow the WHO recommended protocol when using the standard shorter regimen.
- Currently, WHO inclusion criteria for STR are as follows: if there is evidence of resistance to a medicine in the shorter MDR-TB regimen (excluding resistance to isoniazid), then do not use the STR; it is not recommended to base treatment decisions on the DST for ethambutol, owing to the unreliable nature of the tests. Resistance to pyrazinamide (PZA) is difficult to determine. Such resistance is complex, as there are many mutations and it is unknown what the mutations mean. Patients should not be deprived of shorter regimens with PZA due to the results of a test with limited validity. Results on solid media are not reliable; however, results from liquid media with external quality control can be trusted. There is no gold standard for molecular testing of PZA, which makes the process challenging. A draft study is underway in 7 regional laboratories in Belarus and 9 or 10 additional laboratories in the Stockholm Network. Results improved significantly when quality assurance for PZA testing was put in place. The *katG* mutations in MTB are associated with resistance to high-dose isoniazid. MIC for clofazimine (CFZ) was recently endorsed by WHO, but reliability and reproducibility of DST to this drug are still being evaluated. As a result, decisions on inclusion in STR mainly rely on the exclusion of resistance to both fluoroquinolones and second-line injectable TB medicines.
- A clear eligibility criterion for the STR should be included in the next WHO guidelines.
- There is a need to look for alternative regimens with available and reliable DST.
- Countries rarely use moxifloxacin (MFX) 800 mg in the STR, instead MFX 400 mg is applied. The concern is mainly about potential QT prolongation. The manufacturer's recommended dosage of MFX is 400 mg per day, for up to 21 days.
- Based on WHO guidelines, 140 patients were recruited for a Médecins Sans Frontières (MSF) observational study in Uzbekistan. They were treated with 400 mg of MFX. The study found similar DST patterns to other studies, with 70% PZA resistance based on liquid culture, 60–70% ethambutol resistance with a majority of isoniazid resistance plus INHA. The patients who had not been treated with SLDs before were subselected and sorted for fluoroquinolone resistance and dual SLD resistance, which resulted in about 40% of RR-TB

patients being included. About 70% of the patients had good outcomes after nine months compared to the longer treatment of 20 or 24 months, which had 65–70% good outcomes. These patients should be closely followed for identification of treatment failure or relapse in order to offer an effective regimen going forward.

- The primary concern for implementing shortened chemotherapy regimens is early relapse, so patients need to be monitored and followed up for 1–2 years. This would improve the credibility of treatment success as an outcome.
- A discussion took place on how to monitor and systematically report shortened chemotherapy regimens. This should be done in the same way as reporting for long-term regimens. WHO has no recommendations on how to report shortened regimens; nevertheless, countries should conduct reporting where relevant. For the Global TB reporting form, a section on treatment outcomes for cohorts on shortened regimens was introduced. The WHO data collection form for the European Region, has a section for treatment outcomes for BDQ, DLM and STR.
- A reminder was given that the only way to update the recommendations is to implement innovation in a controlled manner, with proper patient management, recording and reporting.

Session 3. Operational implementation, presentations and discussion – Experience on introduction of the new drugs/new regimens presented by NTPs

endTB project in Kazakhstan (Dr Malik Adenov)

The endTB project in Kazakhstan is implemented by Partners in Health (PIH). The project duration is four years with four outputs: expand the use of new TB drugs under close monitoring according to WHO recommendations (observational study); revolutionize MDR-TB treatment (endTB clinical trial); reduce country-level barriers to scale-up the use of new TB drugs; and facilitate the sharing of knowledge and dissemination of evidence. The project was expanded to an additional five regions in July 2017, bringing the total to 10. The drugs (BDQ, DLM, linezolid, clofazimine and imipenem/cilastatin) are funded by PIH and procured through the GDF. A total of 650 MDR/XDR-TB patients are to be enrolled within the endTB project by 30 September 2018. The majority of patients use BDQ and DLM for longer than 24 weeks because of clinical indications. The endTB project is conducting cohort event monitoring, the most advanced stage of active pharmacovigilance. In parallel, PIH and the NTP are introducing other tools focused on improving adherence to therapy, including social support, video observed treatment (VOT) and other types of patient-centred accompaniment. Project results have been promising and are similar to the overall endTB project cohorts. Demand for new drugs is high. Starting in 2019, the new drugs will be procured from national budgets using the GDF mechanism.

endTB project Georgia (Dr Nino Lomtadze/Nana Kiria)

Prior to 2016, Georgia was a high-burden MDR/XDR-TB country. The 2015 cohort had a 56% treatment success rate for RR-TB and XDR-TB. Around 41% of RR-TB patients are eligible for new TB drugs. The observational study presented reviewed patient records and had the primary objectives of: (1) describing patient outcomes and assessing factors associated with unfavourable outcomes (treatment failure, loss to follow-up and death); and (2) estimating the frequency of adverse events of clinical significance. At six months, 243 of 291 patients (84%) had culture conversion. See Box 4 for details on the enrolment and outcomes (Table 2) of the treatment programme in Georgia.

Box 4. Patient enrolment endTB Georgia

- 347 patients enrolled on new treatments
- 254 patients on BDQ, 93 patients on DLM and 67 patients on BDQ/DLM consecutive use
- BDQ and DLM extension for 3–6 more months – 21 patients.

Table 2. Treatment outcomes for 2014–2016 cohort

	2015		2016	
	N	%	N	%
Still under treatment	0	0%	66	42%
Outcomes	146	100%	91	58%
cured	90	62%	48	31%
completed	19	13%	7	4%
died	9	6%	9	6%
failed	9	6%	13	8%
lost to follow-up	18	12%	11	7%
not evaluated	1	1%	3	2%
TOTAL	146	100%	157	100%

Challenge TB Project in Uzbekistan (Dr Nargiza Parpieva)

Challenge TB is funded by USAID and is being implemented by the WHO Country Office in Uzbekistan in 2016–2019. The areas of implementation include universal access to health-care services, TB laboratory services, infection control, health system strengthening, monitoring and evaluation, and surveillance. Patient enrolment began in June 2018 in two regions. A patient triage approach is applied using rapid molecular tests, early detection of resistance and early initiation of effective regimens. All patients with XDR-TB receive individualized regimens. Pharmacovigilance is applied according to WHO recommendations, with a focus on proper aDSM activities. The Parliament supported the scale-up of pharmacovigilance, as they would like to improve pharmacovigilance for other diseases as well.

MSF/NTP project in Tajikistan (Dr Firuz Sharipov)

Treatment success in Tajikistan is 53%, with an 8% treatment failure rate. Additional regions have been added to the project this year. The project covers 48% of the general population. The focus has been on improving the sputum transportation system, diagnostic algorithms and introducing clinical and programmatic monitoring to improve management of cases and monitoring and supervision. Activities include developing standard operating procedures (SOPs) on collection, storage and transport of sputum; procurement of fridges for sputum storage; and training of TB centre experts and health-care workers at the primary care level on sputum collection and storage. The project established a system of drug safety monitoring to ensure timely detection of adverse reactions. The primary outcomes include the development of regulatory documents for project activities and of clinical protocols and SOPs. As of May 2018, 224 patients were enrolled and 28 had already been successfully treated. See Box 5 for a summary of preliminary results.

Box 5. Summary of preliminary results – MSF/NTP Tajikistan

- 71% cure rate
- 6.5% treatment failure rate
- 6.5% lost to follow-up.

Summary of questions and comments

- Infection control is a central part of people-centred care. Countries have taken steps for infection control, such as separating MDR-TB, pre-XDR-TB and XDR-TB patients. After sputum conversion, the patients are transferred from smear positive to negative areas. Some patients are started on outpatient treatment (if they meet eligibility criteria) and countries have been able to reduce the length of hospital stay.
- In Kazakhstan the enrolment phase of the endTB project will finish on 30 September 2018. Following that, enrolment will be continued within Global Fund and government funding (starting in 2019). PIH, through the endTB project, provided extensive technical support to the NTP and regional TB services.
- Only a small number of patients had QT prolongation of more than 500 – within the endTB project.
- DLM was mostly used in paediatric cases and patients with HIV coinfection.
- BDQ was used for the first six months in the past, as countries did not have the recommended 4–5 effective drugs needed. With BDQ, culture conversion occurred in month 1–2. When there were no more options, DLM was used, followed by BDQ.
- Several patients who were using new drugs have died, although very few of those could have been related to the use of BDQ.
- BDQ and DLM can be used in combination, but no recommendations are available for combination use. This is not the same as off-label use, as off-label use is the use of BDQ/DLM past six months (as per registration). Patients and clinicians should decide together whether to use the combination.
- There is uncertainty about both long- and short-term regimens; thus, there should not necessarily be a focus on the limitations of short-term regimens as there are also uncertainties about long-term regimens.
- NTPs sometimes expect detailed WHO recommendations, but WHO cannot always provide a high level of detail due to lack of evidence. Countries, NTPs and clinicians must make decisions based on the available information. Deviations from the recommendations should be documented and, if possible, published in English language journals in order for WHO to include the findings in recommendation updates.

Session 4. Presentations and discussion on drugs selection and adoption of new regimens

Indications for the new TB drugs and selection of the drugs for development of an effective regimen (Dr Askar Yedilbayev)

The 2016 WHO guidelines recommend at least five effective TB medicines during the intensive phase. More experience has been accumulated on the use of BDQ than DLM in treatment of XDR-TB. Anti-TB drugs are likely to be effective if: the drug has not been used in a regimen which failed to cure the individual patient; DST performed on the patient's strain indicates that it is susceptible to the drug; no resistance is known of to drugs with high cross-resistance (e.g. resistance to kanamycin is highly associated with resistance to amikacin); the patient has no known close contacts with resistance to the drug; drugs resistance surveys (DRS) demonstrate that resistance to the drug is rare in patients with a similar history. These factors should be considered by appropriate committees and boards when determining when to use new drugs. DLM has a great safety profile and has no interactions with antiretroviral drugs. The use of BDQ and DLM beyond 24 weeks can be applied when less than five effective drugs are in the regimen.

Detailed guidelines on eligibility criteria, dosing, regimen design, drug–drug interactions and other relevant information is available in the *endTB clinical and programmatic guide for patient management with new TB drugs*⁸.

⁸ EndTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. EndTB Consortium. Version 4.0; January 2018. (<http://www.endtb.org/sites/default/files/2018-02/Guide%20for%20New%20TB%20Drugs%20Version%204.0%20final.pdf>, accessed July 1 2018).

The endTB observational study includes 17 countries and more than 2650 patients. BDQ prescription started a full year prior to DLM; however, the use of DLM has increased and prescription rates of the two drugs are now similar. For patients on BDQ or DLM, an 82% six-month culture conversion was achieved for the first cohort of patients analysed, who were enrolled between 1 April 2015 and 30 September 2016. A 73% six-month culture conversion rate was achieved for patients on combined use of BDQ and DLM, and 80% for XDR-TB patients. The preliminary conclusions are: conversion percentages are favourable in a cohort of treatment-experienced patients with high-grade resistance and extensive disease; early deaths among patients with advanced HIV drive slightly lower conversion percentages among patients with HIV; and patients who convert appear to do well, with low rates of reversion and death (this will be confirmed in a larger sample). Despite initial discomfort and lack of knowledge about the new TB drugs, clinicians are rapidly starting to use them once barriers have been removed. If they have access, clinicians like to prescribe both DLM and BDQ. The new TB drugs are becoming “mainstreamed” in endTB countries. The drugs were initially restricted only to a few patients with extensive drug resistance, but now they are increasingly used for patients who are intolerant to conventional MDR-TB drugs, they are commonly used in patients with comorbidities (hepatitis C, diabetes, HIV), and are increasingly used together (concomitant use) and in children.

Summary of questions and comments

- WHO guidelines state that five drugs must be used for effective treatment for XDR-TB. Is it possible that four drugs are sufficient in situations where five drugs are difficult to access? The need for five drugs will be reviewed during the revision of the WHO guidelines later this year.
- Up to 80% of patients had history of the use of a SLD. The range of drug resistance was quite broad, and many laboratories cannot perform DST for PZA. Therefore, the data is slightly uncertain.
- WHO guidelines attempt to simplify the recommendations; however, in certain challenging cases, countries may need additional advice. The European Respiratory Society initiated the TB Consilium for countries to contact experts and receive a response within a short time period (typically 24 hours). The site is moderated by a WHO collaborative centre. Not many people use the tool; however, it will continue to be available to countries as it is very useful.

Session 5. Procurement and supply management, presentation and discussion

Stop TB Partnership’s Global Drug Facility (GDF): uptake of new TB tools in line with the transitioning to domestic financing in the WHO European Region (Dr Maya Kavtaradze, Dr Andrei Mosneaga)

All drugs and diagnostic tools for TB treatment are available through the GDF. The GDF can also provide technical support, including access to software. The only country that has procured rifapentine is Estonia, even though WHO recommends the use of rifapentine for children and adults. It can be used once a week for six weeks. A bidding process with the manufacturer reduced the price and now one treatment of rifapentine costs US\$ 45. If countries procure directly from the manufacturer the price is significantly higher. The EECA region is the highest priority for the GDF. More than 23 000 treatments of BDQ and DLM have been delivered globally. The demand for BDQ is higher than for DLM, perhaps because BDQ is free or because countries and clinicians prefer treating with BDQ.

TB in children is often underprioritized. The GDF has led the roll out of new second line paediatric formulations, however, uptake is slow. Paediatric formulations can be procured through the GDF. Worldwide, 81 countries (8 in EECA) have ordered around 700 000 treatment courses.

Challenges in the introduction of new TB tools are outlined below.

- The EECA region has begun the shift to domestic financing and procurement of pharmaceuticals and diagnostics, and other regions will follow. Local capacity is lacking in procuring quality assured drugs and diagnostic tools. Drug registration is a challenge, as national procurement is not possible if drugs are not registered. New TB drugs are not on the list of essential medicines in most countries, which is a barrier to initiating procurement. Through the GDF, countries can procure drugs at a lower price. The Global Fund does not allow countries to procure locally produced drugs (with unknown quality) and procurement of drugs through the GDF, from prequalified suppliers, is encouraged. It is critical to include quality assurance in procurement processes.
- The GDF faced a major challenge with countries ordering imipenem for 12–24 months and then not using the drug after all. This can cause stock issues and is a waste of limited resources. Countries should increase procurement frequency to avoid this situation.
- No countries have updated electronic health information systems, meaning that countries must rely on physicians to monitor adherence. Local capacity in quantification and forecasting needs to be strengthened, as weak supply chains affect drug availability.
- There should be approvals for removal of obsolete “old” drugs.
- Procurement and supply management (PSM) support on diagnostics is insufficient.
- Information is insufficient on the isoniazid preventive therapy (IPT) for latent TB infection, rifapentine use and DR-TB formulations for children.
- Overall weak PSM systems hamper the availability of medicines at all levels.

Summary of questions and comments

- Countries need support to quickly register drugs, so as not to rely on customs to work quickly. In some cases, drugs are held in customs for up to six months, which undermines TB programmes. NTPs are not always able to influence authorities, hence WHO recommends promoting WHO prequalification.
- BDQ was registered in Ukraine as of 18 June 2018, which is a great success. It took more than one year to register the drug, indicating to other countries that the process can be lengthy.
- A question was asked as to whether the GDF will consider inclusion of devices such as catheters and ports. Countries currently purchase these devices using Global Fund support; however, after withdrawal of the Global Fund it may be difficult for countries to procure. The GDF can procure devices at a lower price but must have an estimation of the needs. Therefore, they are not yet included in the catalogue.
- The GDF can participate in bidding processes, as long as they are informed in advance and the restrictions from the countries are limited.
- The GDF collaborates with manufacturers to reduce minimum procurement quantities. There is currently no minimum procurement quantity for second-line paediatric TB drugs.
- Depending on the drug, an emergency order to the GDF will take at least two months.
- In one country, all of the MDR/XDR-TB drugs have been added to the national essential medicines list.
- More information on accelerated registration of WHO prequalified finished pharmaceutical products (FPPs) can be found on the WHO website.⁹

⁹ Accelerated Registration of Prequalified FPPs. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (<https://extranet.who.int/prequal/content/collaborative-registration-faster-registration>, accessed 31 July 2018).

Session 6. Safety aspects in the introduction of new TB drugs and regimens, presentations and discussion

Safety of the new drugs and aDSM as an integral part of the drugs introduction. Experience of Belarus (Dr Alena Skrahina, Ms Svetlana Setkina)

In 2017, Belarus had a TB incidence of 24.3/100 000 and mortality of 3.2/100 000. Of MDR-TB cases, 66% have been previously treated and 33% are new. Among the 2014 cohort, the success rate was 54% for MDR-TB and 36% for among XDR-TB patients. The 2015 cohort improved to 64% success for MDR-TB and 53% success for XDR-TB. The number of HIV/TB coinfecting patients has increased and more than 50% of HIV/TB cases have MDR-TB. Among HIV positive patients who have previously been treated for TB, the MDR/XDR-TB rate is 100%. Results from a study on resistance of *Mycobacterium tuberculosis* isolates to pyrazinamide and fluoroquinolones found that 81% of all RR-TB patients are resistant to pyrazinamide.¹⁰

One of the key strategic directions of the National Strategic Plan (NSP) is the rapid uptake of new drugs and regimens. Since 2012, the country has been generating evidence through cohort monitoring of various medicines among assorted subpopulations. Molecular diagnosis has been scaled up. Work is ongoing to ensure early access to new TB drugs. New drugs are being used without national registration or authorization. Task forces and a technical working group have been established for the introduction of new drugs in the NTP. The technical working group includes the NTP, national pharmacology control (NPC) specialists and one person in every region who is responsible for implementation of active drug safety monitoring. The established inclusion criteria make it possible to provide treatment with new anti-TB drugs for almost all patients with pre-XDR-TB and XDR-TB. VOT has been successful. Port systems are widely used for patients on imipenem. Half of these patients have MDR-TB and the other half are MDR susceptible. This approach has been very successful.

The introduction of aDSM has supported the timely detection of all adverse reactions. Initially, the system was not adapted for safety monitoring of certain types of new drugs. Active safety monitoring of new drugs had two phases: at the initial stage of introduction, cohort event monitoring was implemented; currently, model of active drug safety monitoring, (intermediate package) is used for patient safety monitoring and adverse drug reaction (ADR) data collection. The NTP/NCP joint expert committee performs routine CEM safety data analysis for the intermediate CEM report. An rGLC expert is involved in data analysis. The analysis will be available upon finalization. Most patients only had mild or moderate ADRs. All patients experienced a minimum of one ADR; most were mild to moderate in severity and reversible. About 10% of patients experienced serious ADRs. Most of the SAEs were cardiovascular disorders. The cohort using DLM has had five deaths, which were attributed to other conditions, including HIV and cancer. The data has revealed that alcohol abuse is a major barrier to treatment success. Alcohol abuse was identified as one of the common factors aggravating BDQ cardiotoxicity. About 50% of patients had at least one episode of QTcF prolongation. This was mostly a mild severity of prolongation of up to 480 ms. No more than 6% had prolongation exceeding 500 ms. Cardiac toxicity is the most significant potential ADR for BDQ, including proarrhythmogenic and cardiomyotoxic action, which in some cases could lead to the development of serious ADRs. Proper aDSM requires adequate physician training. Guidance on how to manage adverse reactions is critical, as most physicians are not experienced in management of new TB drug related ADRs. This requires monitoring from NTP managers. aDSM is needed to change the current routine clinical practice and create adequate conditions for the use of new TB drugs with a positive risk–benefit ratio for patients. The Belarus study concluded that treatment of MDR/XDR-TB with BDQ and DLM has a reasonable

¹⁰ Zignol M, Dean A, Alikhanova N, Andres S, Cabibbe A, Cirillo D et al. Population-based resistance of *Mycobacterium tuberculosis* isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. *Lancet Infect Dis.* 2016;16(10):1185–1192 ([https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(16\)30190-6/abstract](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)30190-6/abstract), accessed 31 July 2018).

safety profile, quick sputum smear and culture conversion, and high treatment success rates (88.3%) (see Box 6 for a summary of treatment results and Table 3 for data on drug safety).

Box 6. Summary of preliminary results of BDQ and DLM use for MDR/XDR-TB patients in Belarus

- 715 patients, including 31 children and adolescents (as of March 2018)
- 501 patients on BDQ, 176 patients on DLM, and 38 patients on BDQ+DLM regimens
- treatment success (BDQ/DLM): 181/3
- treatment failure (BDQ/DLM): 3/2
- lost to follow-up (BDQ/DLM): 13/3
- died (BDQ/DLM/BDQ+DLM): 8/2/1
- treatment ongoing (BDQ/DLM): 336/167

Table 3. Preliminary data on drug safety of BDQ and DLM in Belarus

	BDQ	DLM
Adverse events and serious adverse events	100% of patients – mild to moderate 10.3% – serious	91% of patients – mild to moderate 10% – serious
Serious adverse events		
Cardiovascular disorders	30% of SAEs: increased QTcF, arrhythmia, cardiac failure	1 case: increased QT
Serum electrolytes disorders	20% of SAEs: hypotassaemia, hypomagnesemia, hypocalcaemia	1 case: hypotassaemia
Central nervous system disorders	20% of SAEs: seizures, cerebral stroke, status epilepticus	
Renal and urinary tract disorders	15% of SAEs: toxic nephropathy	
Hepatobiliary disorders	10% of SAEs: toxic hepatitis	
Immune system disorders	5% of SAEs: angioedema	1 case: anaphylactic shock
Psychiatric disorders	5% of SAEs: agitation	
Infections and infestations		1 case: meningoencephalitis

Summary of questions and comments

- The majority of information for causality assessments is submitted to the national pharmacovigilance centre. The primary assessment is made by the clinician and then repeated at the national pharmacovigilance centre. Cases in doubt are discussed by the TB Consilium. Patients with SAEs are followed up for 24 months within the cohort monitoring. Longer follow-up is conducted if needed. With support of the MoH, training and monitoring was routine with projects. Routine pharmacovigilance is included in national guidelines.
- QT prolongation was correlated in some cases with risk factors, however, one of the common risk factors for QT prolongation was identified as alcohol abuse.
- Safety reports are sent to the WHO ADRs database (Vigibase) and Global aDSM database.
- Registration of BDQ in Belarus will be achieved shortly through a Russian Federation company.

WHO statement on off-label use of TB medicines (Dr Ernesto Jaramillo)

Drug regulatory authorities allow the marketing of medicines developed by drug manufacturers based on specific information on the efficacy and safety of the product, including dosage and length of use for the

treatment of specific conditions. Off-label use refers to the use of the drug outside the conditions and indications for which the products were registered. Manufacturers often do not update labels, as it is costly and time consuming to conduct phase III trials for a label update, especially when investments to update the label may not be recovered from the marketing of the product. Off-label use is an acceptable practice, as long as it is done properly.

Thus, the use of BDQ and DLM beyond what regulators have approved (six months) is considered off-label use. It is known that MDR-TB patients need treatment for more than six months (9–12 months for shorter regimens, and 20 in the longer regimen), which is longer than the approved six-month use. However, clinicians and patients should jointly assess the options whenever off-label use is needed and make a decision in the face of uncertainty about the harms and benefits, but certainty about the high lethality of MDR-TB if treated with a substandard regimen. It is unknown whether the developers of BDQ and DLM plan to conduct clinical trials for evaluating the use of BDQ and DLM past six months. Therefore, it becomes paramount that data on safety and effectiveness of use past six months is collected and submitted. aDSM should be strengthened to ensure the collection of quality data to inform policy updates on off-label use.

Session 7. Planning operational research

Development of the study protocols for the modified shorter treatment regimens and GDI Core Group generic protocol for operational research on novel shorter regimens (Dr Askar Yedilbayev and Dr Andrei Dadu)

There are concerns about the current WHO shorter treatment regimen (STR), as the STREAM trial revealed slightly worse outcomes compared to the 20-month regimen and no clear toxicity benefit. Concerns under programmatic conditions include that it is difficult to determine which patients have SLD resistance, the rate of adverse events is high and follow-up may not quickly detect patients with ototoxicity or treatment failure. Some countries are attempting to adjust regimens at country level. Results from the STREAM phase II clinical trial are expected to be finalized in 2021. Countries should be able to implement a number of novel regimens that are shorter and are currently being tested in clinical trials, through operational research. If countries are already adjusting STREAM regimens, they may as well be encouraged to use STREAM C under operational research conditions, as it is better to use a regimen that is under evaluation than to use something completely new.

The Global Drug-resistant TB Initiative (GDI) recently developed a standard protocol for implementing regimens from clinical trials in operational research.¹¹ Most of the drugs are commercially available and can be used in operational research. The primary objective is to determine the treatment outcomes of patients who are treated with novel shorter MDR-TB regimens.

Summary of questions and comments

- It is important for countries to implement operational research based on well-documented protocols and convey ethical principles review, in order to create and share standardized, good-quality data that can be used to inform recommendations. The ERI-TB is available to facilitate the provision of such operational research in countries of the European Region. It would be useful to have an electronic questionnaire for operational research linked to this protocol. Some countries have electronic databases that could be used.
- Although quality operational research can be used as evidence to inform recommendations, these studies are not clinical trials.

¹¹ The evaluation of effectiveness and safety of novel shorter treatment regimens for multidrug-resistant tuberculosis: Operational research protocol template. Geneva: Global Drug-resistant TB Initiative; 2018. (<http://www.stoptb.org/wg/mdrtb/resources.asp>, accessed 1 August 2018).

- The compassionate use of drugs should be considered in cases of children or dying patients who have no other options. In these cases, operational research guidelines should be used.
- The timeline for approval and adoption of shorter treatment regimen (STR) depends on the country.
- WHO endorsed STREAM regimens B and C at different times, as with regimen B nearly all countries were able to test for resistance. With STREAM C, it is critical that countries can perform DST of BDQ at baseline and follow-up, which is assumed to be included in the operational research protocol.
- South Africa has changed their national protocol and replaced injectables with BDQ. The country has good infrastructure for collecting and analysing data and actively collaborates with WHO to develop evidence. Other countries could do the same, if they have the capacity to collect quality data on the recommendation deviance.
- It is sometimes difficult to recruit patients for trials. The STREAM clinical trial does not include patients from the EECA region, so it is important to have operational research in this region. New partners should be encouraged to work with partners who have been present in the region for many years.

Session 8: Laboratory aspects

Laboratory aspects of the new treatment introduction, including diagnostic algorithm (Dr Gulmira Kalmambetova)

The introduction of new regimens requires the following:

- Development of clinical protocols with the adaptation of the national diagnostic algorithm.
- Training of laboratory specialists and clinicians: laboratory technicians are often requested to interpret laboratory results for clinicians, as they are not adequately trained in reading results. Clinicians must be trained in reading laboratory results. In January 2018, the WHO Regional Office for Europe delivered trainings for clinicians and laboratory specialists in Kyrgyzstan on the introduction and scale-up of new drugs.
- Transportation of samples with a referral system: within the primary health care level to expert laboratories and from primary health care laboratories to the reference laboratory, where cultures and DST are performed.
- Availability of the laboratory network: the network should be well equipped, trained, and able to track adverse events.
- Harmonization of financial mechanisms for laboratories: there is a challenge in financing laboratories and finding a balance between only a few people tested at high quality or more people tested at low quality.
- Revision of reporting forms: reporting should be followed up and monitored by laboratories.
- Improvement/acceleration of the transfer of laboratory results to clinicians: susceptibility cases must be quickly communicated to clinicians. One way is to implement encoding systems to transfer results by email.
- Electronic database systems for TB patients with a laboratory module.

Summary of questions and comments

- It is vital that laboratory results are quickly communicated, as clinicians often disregard slow results.
- Clinicians do not necessarily base treatment on DST results. This is problematic for the GDF, as the mechanism procures according to orders, which does not always align with the reality in country.
- The training toolkit used in Kyrgyzstan will soon be published online for laboratory specialists and clinicians.
- When countries shift to national financing they may save in the short term by not using expensive diagnostic algorithms, but missing an MDR-TB case has a much higher financial and public health cost.
- When clinicians do not understand the laboratory results, they may pay attention to certain subgroups of data. It is important to use a joint approach with clinicians and laboratory technicians by using a

standardized form. Some countries may already use such a form and are welcome to share it with others if it is available.

- Some countries have attempted to get test results in various formats and have developed an optimal form.
- There are three priorities in laboratory diagnostics:
 - Timely and quality detection of TB and DR-TB in all areas of all countries: ELI can support this work.
 - Building capacity in national and regional reference laboratories: Laboratories should take on more extensive tasks. Laboratories should be able to test for BDQ susceptibility. Focus should be placed on building capacities of national reference laboratories to ensure sustainability. Capacity for research laboratories to conduct operational research should be improved.
 - Increased communication between laboratory experts, clinicians, grant givers and other stakeholders: The role of laboratories has changed and clinicians and NTPs should demand more from them. Clear terms of reference and allocated budgets for national reference laboratories should be developed. Laboratory result forms change often, and clinicians may need support in interpreting results. Particularly as programmes move towards precision medicine, it is critical that laboratory results are interpreted correctly.
- Some discussion took place on whether it was necessary for clinicians to receive results of gene mutations, such as katG. It was suggested that clinicians should receive the results, as it will support record keeping of mutations. ELI includes gene mutations on the forms, as laboratory technicians and clinicians should discuss the mutations, especially if discordant results are discovered.

Session 9: Infection control

Infection control guidelines development update – WHO policy on infection prevention and control in clinical and programmatic management of tuberculosis (Ms Lice Gonzalez-Angulo)

The presentation focused on the WHO policy review process. The endTB strategy is built on three pillars: (1) integrated, patient-centred TB care and prevention; (2) bold policies and supportive systems; and (3) intensified research and innovation. Infection control is built into pillar two (bold policies and supportive systems) and works on strengthening political commitment and working with advocacy groups. In addition, work is ongoing to implement universal health coverage policies and regulatory frameworks to support quality control and rational use of medicine. In order to succeed at prevention, it is necessary to implement all sets of controls together. In 2016, WHO policies on infection control was published that sets core components for infection prevention and control. The WHO Guidelines on Infection Prevention and Control in TB updated policy will be released in second half of 2018.

Summary of questions and comments

- WHO has no plans to update the biosafety in TB laboratory manual with new recommendations in the short term.
- This policy update is based on all available evidence, and will also attempt to harmonise with the 2016 “Core Components” document.
- Countries use treatment as an infection control measure and there is anecdotal evidence that patients are becoming not infectious in the first two days of treatment. One of the questions that guided the review of TB IPC guidelines was focused on effect of appropriate treatment on infectiousness of patients.

Session 10. DR-TB treatment outcomes in the EECA region

Findings and recommendations of a study on determinants of DR-TB treatment outcomes in the EECA region (Dr Christian Auer)

The study was funded by the Global Fund. Treatment success was only 29%. The study used mixed methods and included a desk review, Delphi survey, interviews and focus group discussions with patients and health-care workers, and a review of patient charts. Box 7 presents a summary of findings of the study.

Box 7. Summary of findings of the study on the determinants of DR-TB treatment outcomes in the EECA region

- The desk review had six main topics: subpopulations, patient enablers, provider enablers, challenges to treatment completion, recommendations on treatment outcomes, and other notes on treatment outcomes.
- Delphi study key findings:
 - The biggest factors for promoting successful treatment outcomes for individual DR-TB patients are that patients receive rapid diagnosis and treatment, and that they receive adequate social, financial and nutritional support. For DR-TB patients' families and communities the biggest factor in promoting successful treatment outcomes was that the economic situation of the family was not worsened by the patient's illness or treatment.
 - Only one expert felt that the TB community should seriously consider adopting the STR.
- Patient chart review key findings:
 - 212 patient charts were reviewed: 71% were male, 25% were employed when they were diagnosed with DR-TB. At baseline, 30.2% had a history of regular alcohol consumption, 5.2% used illicit drugs, 10.8% had a history of detention and 7.1% were homeless.
 - 21.7% of the patients had pre-XDR-TB and 9% had XDR-TB.
 - At two months of treatment, 56% had a negative culture status.
 - The primary determinants of poor treatment outcomes were whether the patient had: previous SLD treatment, a BMI below 18.5, bilateral disease with more than one cavity, homelessness in the past or at baseline, alcohol consumption at baseline, and culture positivity at two months.

The key lessons learned were as follows:

- Alcoholics are not given sufficient attention and homeless people need comprehensive support.
- Home-based directly observed treatment and decentralized treatment are crucial.
- Twenty months of treatment with side effects is barely tolerable and shorter regimens and new drugs are critical.
- Many of the challenges and recommendations involve programme management issues.
- One third were culture positive at two months and at high risk of adverse treatment outcomes.

Primary recommendations were as follows:

- Social support including enablers, patient-centred treatment, shorter regimens and new TB drugs are crucial to improve DR-TB treatment outcomes and should be scaled up urgently.
- Key populations with DR-TB, including homeless people, alcohol and drug users, and migrants/refugees should receive appropriate support and attention.
- More resources from both domestic and external sources are required to scale up interventions that contribute to better treatment outcomes.

Summary of questions and comments

- The patient chart analysis was not statistically significant due to the small patient sample; nonetheless, the findings give an overall impression. Some countries may want to verify the findings in their context. Triangulation on the importance of social support was conducted on the Delphi survey.
- It was recognised that the primary findings were regarding social support and the need for people-centred care. Drugs alone will not provide success. Treatment of comorbidities, such as mental health, needs to be integrated into TB treatment.

Session 11. Protocols

Drafting the protocols – summary (Dr Masoud Dara and Dr Ogtay Gozalov)

In his summary to the workshop, Dr Ogtay concluded that only 5–10% of patients are started on shortened chemo-regimens even though, in practice, 50% are eligible. There is a high appreciation on the selection of the appropriate and effective chemo-regimens, but this should be based on laboratory data prior to initiation of the treatment. Active drug safety is critical. He noted that the rGLC recommendations are only a starting point for treatment.

Dr Dara reminded participants that the Region has only a 55% cure rate for MDR-TB, which is not high enough. Access to medicine needs to be scaled up and more operational research conducted on developing the better models of care delivery. There is a high opportunity to address social determinants, such as alcohol, tobacco, and diabetes for the countries while implementing their NSP's and include the appropriate messages for advocacy at thigh level. On 9 May 2018, all United Nations agencies signed a position paper on working on more than just medical care, but also including social determinants. This will be piloted in three countries of the EECA region. The rGLC's role is to facilitate the work of countries, and it is available to write to and meet with ministries if necessary. The messages from the rGLC/Europe to the UNHLM on TB (26 September 2018, New York), will be considered for the final version of the resolution.

Conclusions

The following conclusions were drawn from the face-to-face meeting and workshop:

- Treatment outcomes in the Region are improving, thanks to Member States and international partners, including the Global Fund, the GDF, the endTB project (MSF, PIH) and USAID. However, in order to achieve targets for MDR/XDR-TB, Member States and partners must scale up the work being done.
- Medicines alone are not sufficient to ensure successful treatment outcomes. It is necessary for countries in the region to scale up people-centred care approaches, including, but not limited to, social support mechanisms, financial support for transport and adequate nutrition, care for those who abuse alcohol, support for homeless patients, and community-based care.
- The purpose of rGLC missions is now focused on providing technical support to countries, rather than monitoring country activities. In order to provide adequate support, countries should specify mission needs in advance, including the mission focus topics, length of mission, and key stakeholders to engage with.
- The retreat of the Global Fund is a major challenge, as the Region has a high burden of MDR/XDR-TB. Countries that cannot provide financial and human resources within national budgets risk losing ground on progress already made. Quality of care is of great concern, as countries may procure less expensive and lower quality medications, diagnostic tools and other items, when the Global Fund funding is no longer available.
- Member States and partners are encouraged to provide high-quality data and evidence regarding the use of “new” TB drugs and shortened regimens. WHO cannot update recommendations on the use of BDQ and DLM or shortened treatment regimens without more good-quality data, and therefore relies on counterparts and partners to provide them. The rGLC together with ERI-TB can support NTPs who wish to conduct research.
- The UNHLM on TB in September is a great opportunity to highlight the ongoing need to address MDR/XDR-TB in the EECA region.
- Off-label use (i.e. the use of BDQ and DLM beyond six-months) is acceptable, when it is in the best interest of the patient and is agreed upon by the clinician and patient. Off-label use should be accurately monitored and reported in order to increase the evidence base for recommendation updates.

Recommendations of the rGLC/Europe face-to-face meeting, 18–20 June 2018

Recommendations for WHO

1. Continue to search for additional funding to enlarge the rGLC/Europe Secretariat (from 2017 rGLC meeting).
2. Establish a volunteer group to coordinate research in the Region and move forward with a mapping and multicountry mapping study. Countries that have the capacity should take the lead. The meetings can take place via WebEx.
3. Investigate opportunities and support countries to request funding from the Global Fund to conduct evidence generation activities for shorter treatment regimens, as the drugs have been used in the Region for several years but systematic evidence generation has not taken place.
4. Support NTPs to develop an estimate of the number of children with MDR/XDR-TB per country for the GDF to improve procurement services for children's drugs and increase the diagnosis and treatment of children.
5. Organize a webinar for NTPs on the available paediatric formulations for MDR/XDR-TB.
6. With support from the WHO health system strengthening unit, promote WHO prequalification in country to ensure that drugs and diagnostic tools procured under national budgets are of high quality. Translate the WHO drug prequalification documents into Russian for NTPs to advocate for prequalification with local authorities.
7. Organize a WebEx meeting with the assigned consultant and the NTP 2–3 months prior to each mission to finalize the terms of reference and for NTPs to set the limits, expectations and programme for the mission.
8. Prepare key messages, based on the endTB strategy, for NTPs to promote MDR/XDR-TB at the UNHLM on TB.
9. Improve capacity by including trainings or master classes on the country's topic of choice in each rGLC mission. Consider supporting an initiative for engaging high-level experts in missions to improve technical assistance.
10. Create multidisciplinary teams, similar to project HOPE, for a peer-to-peer approach to improve detection of missed cases.
11. Strengthen the capacity of national councils of physicians, particularly at the regional level, and establish monitoring councils in each country.
12. Create an indicator on the number of recommendations addressed from the previous mission to ensure follow-up on recommendations and changing strategies if the approach is not working.
13. Collaborate with the GDF to negotiate with manufacturers to change the procurement of BDQ and DLM from full treatments (six months) to buying loose tablets, as is done with other drugs. Ensure that countries submit official requests to the GDF to influence how manufacturers distribute drugs.
14. Consider nominating a "best practice" country every year as a model for other countries.
15. Based on individual country needs, support NTPs and laboratory managers to include laboratory maintenance and biosafety training in national budgets.
16. Consider developing a framework for treatment outcome proxies (i.e. culture conversion, number of people defaulting, deaths) to be used systematically across the Region.
17. Continue to encourage countries and provide technical assistance on updating the national action plans and advise on substantial increases in national funding for MDR/XDR-TB.
18. Develop a system so that all countries and laboratories that detect resistance keep the resistance isolates for further evaluations through molecular test systems.
19. Actively advocate for inclusion of new drugs into the essential medicines list.
20. Promote the use of the TB Consilium when difficult cases arise.
21. Share the United Nations joint position paper on TB and STREAM C operational research protocol in English and Russian with all meeting participants.

22. ELI should support diagnostics by analysing rGLC reports and determining areas for improvement that are present in all countries.

Recommendations for partners

- All partners and Member States should share names of potential consultants for missions with the rGLC, in order to enlarge the pool of trained consultants. Consultants trained in pharmacovigilance are particularly needed.
- NTPs should specify their precise mission needs (including area of focus and length of mission) in advance, to ensure that missions are planned and executed according to the needs of the country. NTPs can select whether mission reports are to be developed in English or Russian but need to inform the rGLC/Europe in advance of their selection.
- WHO prequalification should be promoted to ensure high-quality drugs, particularly after shifting to national financing.
- The recommendations for the UNHLM on TB should be promoted at the highest level in each country's mission to the United Nations.
- Methods of engaging new partners and stakeholders in missions should be considered (e.g. TB/HIV and TB in prisons).
- Partners should collect, analyse and share with WHO data on shorter treatment regimens and off-label use (i.e. BDQ/DLM use beyond six months) to inform recommendation and guideline updates.
- Member States should increase procurement frequency for the GDF to 2–3 times per year, if possible, to allow changes to be implemented more quickly and minimize waste.
- Dr Gunta Dravniece should share the standardized optimized form for HAIN, LPA test results.

Annex 1. Supporting documents

1. Accelerated Registration of Prequalified FPPs. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (<https://extranet.who.int/prequal/content/collaborative-registration-faster-registration>, accessed 31 July 2018).
2. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. Geneva: World Health Organization; 2015. (apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf, accessed 1 August 2018).
3. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014 (http://www.who.int/tb/publications/pmdt_companionhandbook/en/, accessed 1 August 2018).
4. endTB clinical and programmatic guide for patient management with new TB drugs. Version 4.0. EndTB Consortium; 2018 (<http://www.endtb.org/sites/default/files/2018-02/Guide%20for%20New%20TB%20Drugs%20Version%204.0%20final.pdf>, accessed 30 July 2018).
5. Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level. Geneva: World Health Organization; 2016 (<http://www.who.int/gpsc/ipc-components/en/>, accessed 1 August 2018).
6. Moscow Declaration to End TB. Geneva: World Health Organization; 2017 (http://www.who.int/tb/features_archive/Online_Consultation_MinisterialConferenceDeclaration/en/, accessed 1 August 2018).
7. The evaluation of effectiveness and safety of novel shorter treatment regimens for multidrug-resistant tuberculosis: operational research protocol template. Geneva: Global Drug-resistant TB Initiative; 2018. (<http://www.stoptb.org/wg/mdrtb/resources.asp>, accessed 1 August 2018).
8. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization; 2018 (<http://apps.who.int/iris/bitstream/handle/10665/258941/WHO-HTM-TB-2017.20-eng.pdf?sequence=1>, accessed 30 July 2018).
9. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009 (http://www.who.int/tb/publications/2009/infection_control/en/, accessed 1 August 2018).
10. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. October 2016 revision. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1>, accessed 1 August 2018).
11. Zignol M, Dean A, Alikhanova N, Andres S, Cabibbe A, Cirillo D et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. *Lancet Infect Dis.* 2016; 16(10): 1185–1192 ([https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(16\)30190-6/abstract](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)30190-6/abstract), accessed 31 July 2018).

Annex 2. Programme

Face-to-face meeting, 18 June 2018		
09:00–09:30	Introduction <ul style="list-style-type: none"> • Opening • Adoption of agenda, programme and declaration of interests • Briefing on background, purpose and expected outcomes 	Dr Masoud Dara Dr Andrei Maryandyshev (rGLC/Europe Chair)
09:30–10:45	Follow-up on the previous meeting recommendations and updates from rGLC/Europe Secretariat <ul style="list-style-type: none"> • Follow-up on the previous meeting recommendations • Updates from European Tuberculosis Research Initiative • Updates from European TB Laboratory Initiative • Updates on TB-REP regional project 	Dr Ogtay Gozalov Dr Andrei Dadu Dr Soudeh Ehsani
11:00–12:00	Panel discussion 1. Improvement of treatment success of M/XDR-TB and the role of the rGLC/Europe in that	Dr Andrei Mosneaga Dr Kai Blöndal Dr Askar Yedilbayev
12:00–13:00	Panel discussion 2. Messages from the rGLC/Europe to the UNGA on TB	Dr Elmira Gurbanova Dr Andrei Maryandyshev Dr Liga Kuksa
14:00–15:00	Panel discussion 3. Partners and donors on the implementation of the European TB Action Plan	Dr Sevim Ahmedov Dr Dumitru Laticevschi
15:15–16:00	Panel discussion 4. Development of recommendations to WHO and the rGLC/Europe	Dr Askar Yedilbayev Dr Kai Blöndal Dr Andrei Mosneaga
17:00–17:30	Closure of the meeting	Dr Masoud Dara
Workshop, 19 June 2018		
09:00–09:30	Introduction <ul style="list-style-type: none"> • Opening • Adoption of agenda and programme • Briefing on background, purpose and expected outcomes 	Dr Masoud Dara Dr Andrei Maryandyshev (rGLC/Europe Chair) Dr Fuad Mirzayev
09:30–10:30	Session 1. Current policies and status of implementation, presentations and discussion <ul style="list-style-type: none"> • WHO guidelines for management of DR-TB and patient care • Update on endTB project (global and regional) • Unitaid: continued commitment to improving cure rates for people affected by MDR-TB 	Dr Ernesto Jaramillo Dr KJ Seung Ms Ekaterina Rykovanova
11:00–11:30	Session 2: Status of introduction of Short treatment regimens and steps required to scale it up. <ul style="list-style-type: none"> • Results of the study on resistance profiles and shorter treatment regimen introduction • Indications and steps required for implementation of 	Dr Elmira Gurbanova Dr Liga Kuksa

STR through the prism of the specific epidemiologic
 situation in Europe

11:30–12:30	Session 3. Operational implementation, presentations and discussion. Experience on introduction of the new drugs/new regimens presented by NTPs <ul style="list-style-type: none"> • endTB project in Kazakhstan • endTB project in Georgia • Challenge TB Project in Uzbekistan • MSF/NTP Tajikistan project in Tajikistan 	Dr Malik Adenov (Kazakhstan) Dr Nino Lomtadze/Nana Kiria (Georgia) Dr Nargiza Parpieva (Uzbekistan) Dr Firuz Sharipov (Tajikistan)
14:00–15:00	Session 4. Presentations and discussion on drugs selection and adoption of new regimens <ul style="list-style-type: none"> • Indications for the new TB drugs and selection of the drugs for development of an effective regimen • Example of adoption of new regimens into the national TB guidelines 	Dr Askar Yedilbayev Dr Andrei Maryandyshev
15:30–16:00	Session 5. Procurement and supply management, presentation and discussion <ul style="list-style-type: none"> • Stop TB Partnership’s Global Drugs Facility: uptake of new TB tools in line with the transitioning to domestic financing in the WHO European Region 	Dr Maya Kavtaradze Dr Andrei Mosneaga
16:00–17:00	Session 6. Safety aspects in the introduction of new TB drugs and regimens, presentations and discussion <ul style="list-style-type: none"> • Safety of the new drugs and aDSM as an integral part of the drugs introduction. Experience of Belarus • WHO statement on off-label use of TB medicines 	Dr Alena Skrahina Ms Svetlana Setkina Dr Ernesto Jaramillo

Workshop, 20 June 2018

09:00–10:00	Session 7. Planning operational research <ul style="list-style-type: none"> • Development of the study protocols for the modified shorter treatment regimens • GDI Core Group generic protocol for operational research on novel shorter regimens 	Dr Andrei Dadu Dr KJ Seung
10:00–10:30	Session 8. Laboratory aspects Laboratory aspects of the new treatment introduction, including diagnostic algorithm	Dr Gulmira Kalmambetova
11:00–11:30	Session 9. Infection control guidelines development update	Ms Lice Gonzalez-Angulo
11:30–12:30	Session 10. Findings and recommendations of a study on determinants of DR-TB treatment outcomes in the EECA region	Dr Christian Auer
12:30–13:00	Session 11. Drafting the protocols – summary	Dr Ogtay Gozalov
13:00–13:30	Closure of the workshop	Dr Masoud Dara

Annex 3: List of participants

rGLC/Europe members

Dr Andrei Maryandyshev, Chair
Dr Alena Skrahina
Dr Andrei Mosneaga
Dr Askar Yedilbayev
Dr Elmira Gurbanova
Dr Gunta Dravniece
Dr Liga Kuksa
Dr Jay Achar
Dr Kai Blöndal
Dr Sergii Filippovych
Dr Sven Hoffner

NTP representatives, leading introduction of new medicines/new treatment regimens

Dr Hagigat Kadyrova, NTP Manager, Azerbaijan
Dr Hennadz Hurevich, NTP Manager, Belarus
Dr Nana Kiria, Deputy NTP Manager, Georgia
Dr Nino Lomtadze, responsible for introduction of new drugs and new regimens, Georgia
Dr Malik Adenov, NTP-manager, Kazakhstan
Dr Shakhimurat Ismailov, responsible for introduction of new drugs and new regimens, Kazakhstan
Dr Arnur Nurtayev, Drugs Agency, Kazakhstan
Dr Sofia Alexandru, NTP Manager, Republic of Moldova
Dr Valentina Vilc, Deputy NTP Manager, Republic of Moldova
Dr Adriana Socaci, NTP Manager, Romania
Dr Cristina Popa, Deputy NTP Manager, Romania
Dr Firuz Sharipov, Deputy NTP Manager, Tajikistan
Dr Kurbonkhon Zakirova, responsible for introduction of new drugs and new regimens, Tajikistan
Dr Iana Terleieva, Deputy NTP Manager, Ukraine
Dr Irina Chibisova, responsible for introduction of new drugs and new regimens, Ukraine
Dr Nargiza Parpieva, NTP Manager, Uzbekistan
Dr Barno Abdusamatova, responsible for introduction of new drugs and new regimens, Uzbekistan

Stop TB Partnership/Global Drugs Facility

Dr Maya Kavtaradze

Global Fund to Fight AIDS, Tuberculosis and Malaria

Dr Christian Auer

Unitaid

Ms Ekaterina Rykovanova

endTB project

Dr Askar Yedilbayev

USAID

Dr Sevim Ahmedov, Senior TB Adviser

WHO Regional Office for Europe

Dr Andrei Dadu, Technical Officer
Dr Martin van den Boom, Technical Officer
Dr Masoud Dara, Coordinator
Dr Ogtay Gozalov, Medical Officer
Dr Soudeh Ehsani, Technical Officer
Dr Elena Vovc, Technical Officer
Dr Antons Mozalevskis, Medical Officer
Ms Annemarie Stengaard, Technical Officer
Dr Sayohat Hasanova, Technical Officer
Dr Giorgi Kuchukhidze, Consultant
Ms Efthymia Georgiou, Programme Assistant
Mr Bhim Pradhan, Programme Assistant
Ms Lyudmila Yurastova, Translator
Ms Laura Mandel, Rapporteur
Ms Tatiana Polunina, Translator
Ms Svetlana Setkina, Facilitator
Dr Gulmira Kalmambetova, Facilitator

WHO headquarters

Dr Ernesto Jaramillo
Dr Fuad Mirzayev
Dr Medea Gegia
Ms Lice Angulo Gonzales