Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting: Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region

Copenhagen, Denmark, 25–27 July 2017

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Editors: Masoud Dara and Ogtay Gozalov
Abstract

A workshop on the “Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region” was conducted by the regional Green Light Committee for the WHO European Region (rGLC/Europe) on 25–26 July 2017, followed by a face-to-face meeting on 27 July, in Copenhagen, Denmark. The overall objectives of the 3 days were to exchange experiences and update rGLC/Europe members and consultants on the introduction of new drugs, new treatment regimens and current WHO global and regional policies and initiatives. Participants included members of rGLC/Europe; representatives from the Global Drug Facility, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the TB Europe Coalition, and the United States Agency for International Development (USAID); country representatives from Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Ukraine and Uzbekistan; and staff members from the WHO Global TB Programme and from the joint Tuberculosis, HIV and viral hepatitis Programme of the WHO Regional Office for Europe. A set of recommendations were proposed for WHO and partners from the extensive interactions during the meeting.

KEYWORDS
TUBERCULOSIS,
MULTIDRUG-RESISTANT TUBERCULOSIS,
EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS,
REGIONAL GREEN LIGHT COMMITTEE EUROPE,
BEDAQUILINE,
DELAMANID

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## Abbreviations

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<th>Abbreviation</th>
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<tbody>
<tr>
<td>aDSM</td>
<td>active TB drug safety monitoring and management</td>
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<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
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<td>DR-TB</td>
<td>drug-resistant tuberculosis</td>
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<tr>
<td>DST</td>
<td>drug sensitivity testing</td>
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<tr>
<td>EECA</td>
<td>eastern Europe and central Asia</td>
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<td>ELI</td>
<td>European Tuberculosis Laboratory Initiative</td>
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<td>GDF</td>
<td>Global Drugs Facility</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>ITR</td>
<td>individualized treatment regimen</td>
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<td>LPA</td>
<td>line probe assay</td>
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<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis</td>
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<td>MSF</td>
<td>Médecins Sans Frontières</td>
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<td>MDR/XDR-TB</td>
<td>Multidrug and extensively drug-resistant tuberculosis</td>
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<td>NTP</td>
<td>National Tuberculosis Programme</td>
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<td>PIH</td>
<td>Partners in Health</td>
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<tr>
<td>QTcF</td>
<td>QT interval corrected for heart rate</td>
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<tr>
<td>rGLC/Europe</td>
<td>regional Green Light Committee for the WHO European Region</td>
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<td>RR</td>
<td>rifampicin resistant</td>
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<td>SCR</td>
<td>short course regimen</td>
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<td>SLD</td>
<td>second-line drug</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>VOT</td>
<td>video observed therapy</td>
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<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant tuberculosis</td>
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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 3-day rGLC/Europe meeting was held on 25–27 July 2017 in Copenhagen, Denmark and comprised a regional workshop on the “Introduction of new drugs for drug-resistant tuberculosis treatment in the WHO European Region” and a face-to-face meeting of rGLC/Europe members. The objectives of the meeting were: to update and align regional policies, treatment strategies and regimens according to WHO standards; to share practical experiences; and to provide updates to rGLC/Europe consultants on the use of new drugs and new treatment regimens in the Region.

The meeting was opened by first paying tribute to the memory of Dr Sabine Rüsch-Gerdes (1949–2017). Opening remarks were made by Dr Masoud Dara (WHO Regional Office for Europe, Coordinator, Communicable Diseases; and Programme Manager, Joint Tuberculosis, HIV and viral hepatitis Programme) via WebEx. Dr Andrei Maryandyshev (rGLC/Europe Chair) as the chair of the meeting, welcomed the participants and presented the agenda for approval. Dr Ogtay Gozalov (Medical Officer, Joint Tuberculosis, HIV and viral hepatitis Programme) was the responsible officer for the meeting.

The workshop and meeting were webcast via WebEx for the national tuberculosis (TB) programmes staff and WHO Collaborating Centre for Research and Training in Management of Multidrug-Resistant Tuberculosis in Riga, Latvia. No conflicts of interest were declared by participants.

This report summarizes the presentations and discussions of the 2-day workshop as well as the panel discussions, conclusions and recommendations from the subsequent face-to-face meeting. The agenda of the meeting is included in Annex 1 and the list of participants in Annex 2.
Workshop 25–26 July 2017

Updated WHO guidelines for treatment of drug-susceptible tuberculosis and patient care (Dr Ogtay Gozalov)

The above mentioned updated guidelines were published in March 2017 by the WHO Guidelines Development Group after extensive review by an external review group which included experts from all WHO regions. The document updates the 2010 evidence-based policy guidelines and includes additional GRADE-based recommendations, qualifying the certainty (high, moderate, low, very low) and the strength (strong, conditional) of the scientific evidence on which they are based. The new recommendations are listed under two general headings and are summarized below:

1. Treatment of drug-susceptible tuberculosis

1.1 The 6-month rifampicin-based 2HRZE/4HR is recommended. (No change)
   The 4-month fluoroquinolone-containing regimens should not be used. (Updated)
   **Strong recommendation, moderate certainty in the evidence**

1.2 The use of fixed-dose tablets is recommended over separate drug formulations. (Updated)
   **Conditional recommendation, low certainty in the evidence**

1.3 The use of 3 times-weekly dosing during either the intensive or continuation phase is not recommended. (Updated)
   **Conditional recommendation, very low certainty in the evidence**

1.4 Antiretroviral therapy (ART) should be started in all TB patients living with HIV regardless of their CD4 cell count. TB treatment should be initiated first, followed by ART as soon as possible. (No change)
   **Strong recommendation, high certainty in the evidence**

1.5 A 6-month standard treatment regimen is recommended for people living with HIV and receiving ART. (Updated)
   **Conditional recommendation, very low certainty in the evidence**

1.6 Initial adjuvant corticosteroids should be used to treat TB meningitis. Corticosteroids may be used to treat TB pericarditis. (Updated)
   **Conditional recommendation, very low certainty in the evidence**

1.7 For patients needing retreatment, category II regimen should not be used. Drug sensitivity testing (DST) should be conducted to inform treatment choice. (Updated)
   **Good practice statement**

2. Patient care and support
Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting: Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region

2.1 Counselling, treatment adherence interventions (e.g. food or financial incentives, medication monitors), and treatment administration options (e.g. home/community-based directly observed therapy, video observed therapy) are recommended. (Updated)

Conditional recommendation, low to very low certainty in the evidence

2.2 Decentralization models of care are recommended. (Updated)

Conditional recommendation, very low certainty in the evidence

**The Challenge TB experience in programmatic introduction of new drugs and shorter DR-TB treatment regimens in the WHO European Region (Dr Gunta Dravniece)**

The Challenge TB Project (2015–2019) is the United States Agency for International Development (USAID) flagship TB project and collaborates with the KNCV Tuberculosis Foundation in four countries in the Region (Kyrgyzstan, Tajikistan, Ukraine and Uzbekistan). The project uses a patient triage approach and is based on a diagnostic algorithm with Xpert MTB/RIF, second-line line probe assay (LPA) and phenotypic DST, leading to early and effective TB treatment within 5 days of presentation. Patients with rifampicin-resistant (RR) TB are evaluated for their eligibility to receive bedaquiline-containing individualized treatment regimens (ITR) or the standard DR-TB short course regimen (SCR). The project is closely linked with the bedaquiline donation programme, and other second-line drugs (SLDs) are funded by the United Nations Development Programme (UNDP) and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Donors need to appreciate that advance preparation before enrolling patients is crucial and can take many months. Activities required include: a national guideline review with new drugs added; use of new drugs and new regimens endorsed by the ministry of health to provide the legal framework for registering, importing and using new drugs; active TB drug safety monitoring and management (aDSM) strengthened and linked to the national pharmacovigilance authority; electronic data registration to strengthen patient registration; advanced drug quantification and procurement; full support of international partners; and one uniform and accepted functioning diagnostic algorithm. In addition, local clinical and laboratory staff should receive specific training and supervision (e.g. the dose and frequency of administered bedaquiline can be confusing). The needs of young patients and children should be reviewed. Generic Challenge TB tools and documents also need to be adapted for host countries.

The project in Kyrgyzstan is proving to be very successful. The initial hurdles in Kyrgyzstan were related to practical issues such as delayed drug delivery, transportation of specimens in very mountainous areas, shortage of plasma potassium testing, the lack of an electronic patient database, and lack of sufficient LPA kits. Also, national medical staff was initially very reluctant to the new drugs introduction, but this was overcome after some training. The first patients were enrolled in January 2017. All were smear positive, had received treatment with SLDs and were resistant to fluoroquinolones. A total of 74 patients (including 9 children and 5 adolescents) were enrolled between January and July 2017 for a DR-TB SCR. An additional 82 patients (including 2 adolescents) were enrolled for a bedaquiline-containing ITR.
Other projects are still in the early stages: Tajikistan (40 enrolled for SCR and 40 enrolled for ITR), Ukraine (use of SCR is restricted because of resistance patterns and clofazimine has not been available) and Uzbekistan.

Summary of initial results:
- Cohort size 28 after 5 months of treatment (SCR /ITR)
  - 19 converted to smear negative.
  - 16 are culture negative.
  - Three very sick patients have improved significantly.
  - Two very sick patients died.
- 12 out of 60 patients on SCR switched to continuation phase

Summary of questions and comments
- More details were requested on the project in Kyrgyzstan. All patients in the Kyrgyzstan project will be followed up for 12 months. Sputum culture and chest X-ray will be repeated after the 6th and 12th month. The continuation phase of the regimen has been started on the first culture negative test (BACTEC or Lowenstein-Jensen). In practice, treatment may last longer than 12 months. Drugs used in the SCR included standard doses of capreomycin, moxifloxacin, clofazimine, prothionamide, ethambutol and high-dose isoniazid. The KNCV offline database is temporarily being used for drug safety monitoring.
- Not all countries have easy access second-line DST. Enrolling patients for SCR can be problematic. Opinions varied on the validity of regimens that are based only on the clinical history but which may be necessary (e.g. a decision needs to be made if the patient is very sick). WHO has clear guidelines on this issue. It was agreed that second-line DST is indeed necessary in countries with known very high and varied resistance patterns. It was noted that clinicians have challenged the use of SCR if they do not have access to second-line DST.
- Discordant results. Different results between phenotypic and genotypic DST cause confusion. The European Tuberculosis Laboratory Initiative (ELI) diagnostic algorithm can be used to resolve some of these issues. As a rule of thumb, if any method used detects RR strains then the regime should be changed accordingly and the case investigated further. Test results are communicated to clinicians clearly. ELI is designing a training tool on the interpretation and communication of results, which will be pilot tested in Belarus.

**MSF experience in introduction of new drugs: Clinical aspects and challenges in the introduction of bedaquiline and delamanid (Dr Jay Achar)**

Médecins Sans Frontières (MSF) has a global reach and 50 out of 68 of its TB-related projects focus on the treatment of MDR/XDR-TB. It is also a partner with the endTB Project and TB PRACTECAL. MSF’s experience in the use of new regimens and new drugs is increasing, especially for bedaquiline (1008 patients), delamanid (368 patients) and “off label use” (94 patients on both drugs together; 30 children and adolescents on delamanid; 22 children and adolescents on bedaquiline). Eligibility criteria, ethical approval, patient consent and pharmacovigilance measures
apply for all cases. MSF purchases drugs (e.g. bedaquiline is not sourced from the donation programme).

The MSF SCR consists of an intensive phase of 4–6 months of capreomycin/kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol; and a continuation phase of 5 months of moxifloxacin, prothionamide, clofazimine, pyrazinamide and ethambutol. MSF recognizes the benefit of a shorter duration of treatment (9–11 months vs 20 months) especially in war torn countries. The reduced cost (US$ 3400 vs US$ 520–710) and reduced need for injectables with low toxicity are significant gains to the countries of eastern Europe and central Asia (EECA). Some provision for possible failure and use of other drugs is also necessary.

**Summary of initial results:**

- **Children/adolescents (10–17 years) on bedaquiline**
  - Cohort size 27.
  - 65% culture-positive at baseline.
  - 67% presumed or confirmed XDR-TB.
  - 22 culture-negative after 24 weeks on treatment.
  - Five had prolonged QT interval corrected for heart rate (QTcF) but treatment was not stopped.

- **Bedaquiline/delamanid combination**
  - Cohort size 28.
  - Six culture-positive at baseline.
  - Six culture-negative after month 3.
  - Four culture-negative after month 6.
  - Seven completed week 24 of treatment.

- **Single arm prospective observational study on the use of SCR in EECA**
  - Planned cohort size: 110 MDR-TB patients.
  - 72% “success” at end of treatment.
  - 9% “lost to follow-up”.
  - 16% “failure”.
  - The most common side effects were nausea and vomiting.
  - No severe events occurred.

MSF produced the *Out of Step 2017* report, in collaboration with the Stop TB Partnership, on prevention, testing and treatment policies and practices in 29 countries (8 from the EECA region, excluding Uzbekistan).1

**Summary of questions and comments**

- Some treatment failures occur even if regimens are very well designed. One reason can be amplified resistance.

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1 *Out of Step 2017* can be accessed at [https://www.msfaccess.org/outofstep2017](https://www.msfaccess.org/outofstep2017)
– Loss of the fluoroquinolone component from the regimen is a problem and clofazimine can be useful but is not easily available. Insufficient data is available to recommend the use of bedaquiline instead of a second-line injectable.
– Successful use of bedaquiline and delamanid in combination is still anecdotal. Some dramatic results have been seen in very sick patients. Toxicity concerns remain. “Off label use” of bedaquiline is of some concern, especially since some deaths have been reported among patients, although the drug itself was not thought to have been the direct cause.
– The Global Fund has agreed to replace existing stocks of para-amino salicylic acid as this is no longer recommended by WHO because of patient intolerance to side effects.

**PIH experience on introduction of new drugs (Dr Askar Yedilbayev)**

The endTB Project is funded by UNITAID for 4 years and managed by a consortium of Partners in Health (PIH), MSF and Interactive Research and Development (IRD), with the goal of expanding the use of new TB drugs, revolutionizing the treatment of MDR-TB and generating new evidence to develop and update new treatment guidelines. So far, 2600 patients have been enrolled in 4 years, in a multi-country cohort observational study in 15 countries, including 5 EECA countries (Armenia, Belarus, Georgia, Kazakhstan and Kyrgyzstan). The large cohort size is intended to catalyse the scale-up of access to the new TB drugs and generate evidence on effectiveness and safety. The same clinical approaches and eligibility criteria are used across the whole project. A set of central tools are available for all countries involved in the endTB Project, such as an international medical expert committee for review of problematic clinical cases, and the endTB pharmacovigilance unit responsible for the safety of use of new TB drugs.

The endTB Project in Kazakhstan is implemented by PIH in close collaboration with the Ministry of Health. The introduction of new TB and repurposed companion drugs started in February 2016. Treatment for MDR/XDR-TB comprises ITR, and is based on DST results and other factors, such as history of previous treatment. In 2016, a total of 207 patients in five treatment sites were enrolled to receive bedaquiline (141 patients), delamanid (55 patients) and a combination of both drugs (11 patients). In the majority of cohorts, the use of new drugs is extended beyond the recommended duration (more than 24 weeks) taking into account multiple clinical factors. Quality assured drugs were obtained through the Global Drugs Facility (GDF) using a waiver importation mechanism. Accompanying drugs are linezolid, clofazimine and imipenem/cilastatin.

**Summary of initial results from ITRs in Kazakhstan:**

- Cohort size 207, started therapy between 16 February 2016 and 31 December 2016.
- 90.4% of patients had prior history of treatment with SLDs, 28% had at least one comorbidity other than HIV, 67.7% had bilateral disease, and 82.9% had cavities.
- More than 55% had resistance to fluoroquinolone at baseline (pre-XDR-TB and XDR-TB).
- Linezolid was used in 100% of all ITRs, and clofazimine in 75%.
- 71.6% converted to culture negative after 2 months of treatment with new TB drugs (Range: 91.7% in Astana–64.3% in National Scientific Center of Phthisiology).
- An advanced level of clinical monitoring is provided by PIH to all patients throughout the entire therapy and the safety profile shows good tolerance.
- 30 serious adverse events (SAE) were reported among 23 patients, 9 fatal SAEs among 110 patients.
A pilot project has also been launched in Almaty City for video observed therapy (VOT) outpatient supervised treatment (using Skype, WhatsApp and Viber). An additional supporting mobile unit takes treatment closer to patients’ homes or places of work. The open source Google mapping tool is used to coordinate these activities. A pocket patient-guide on the use of VOT will be available soon.

Summary of questions and comments

- Globally, so far there is little experience in the use of bedaquiline and delamanid beyond 24 weeks, and of their concomitant use. Patients in the Kazakhstan project seem to tolerate extended and concomitant use well. All isolates are being kept in storage, and samples from patients who remain culture-positive by the end of the third month will be sent for DST for new and companion drugs. More updates on the extended and concomitant use of bedaquiline and delamanid are expected soon.
- Alcohol-related problems are very common. Usually, no specific support is available and this behaviour in itself is not a considered a contraindication for enrolment.

Belarus country experience on the introduction of new drugs and new treatment regimens (Dr Alena Skrahina)

Belarus has one of the highest rates of MDR-TB in the Region but a gradual decrease in the number of notified TB cases has occurred since 2008. Data from 2016 show that MDR-TB was present among 68% of those previously treated, and in 36% of new cases. The rate of successful treatment outcomes is poor (success: MDR 54%, XDR 36%) and 17% of XDR-TB cases end in fatality. HIV is becoming an important determining factor and 505 new TB/HIV patients were reported with MDR-TB in 2016; 20% showed XDR strain patterns. Mortality in this group is very high. A total of 1808 MDR-TB patients are receiving treatment in the country, of which 1178 have pre-XDR or XDR-TB.

National TB policies and capacity in Belarus have been strengthened and supported by favourable regulations. The introduction of new TB drugs follows WHO guidelines, laboratory preparedness is improved and the national regulatory pharmacovigilance centre is part of VigiBase™, a database managed by the WHO Collaborating Centre for International Drug Monitoring in Uppsala. A task force and technical working group lead the introduction of new TB drugs and health-care professionals receive intensive training in drug safety. Treatment regimens are approved by the national MDR-TB consilium. As national population-based studies report that 81% of RR strains are also resistant to pyrazinamide and 97% of isoniazid resistant strains are due to the KatG gene mutation, these two drugs (pyrazinamide and high-dose isoniazid, as well as a shorter MDR-TB regimen) are no longer strong options. Implantable central venous access ports make the use of carbapenems and second-line injectables easier and safer.

A prospective cohort study on the use of new drugs among 422 pre-XDR and XDR-TB patients in Belarus is underway (361 on bedaquiline, 56 on delamanid, 5 on both; 23 are children or adolescents). Access to bedaquiline, delamanid and clofazimine was allowed thanks to a single permission waiver with the help of international partners (WHO, the Global Fund and MSF). Ethics
approval and informed consent were obtained and eligibility criteria and contraindications set.\(^2\) The intensive phase of the regimen uses at least five drugs and largely depends on bedaquiline/delamanid, clofazimine, linezolid and terizidone. In total, 208 patients have received bedaquiline or delamanid for more than 6 months, and 168 will continue for more than 1 year. VOT is also being piloted on a sub-set of patients. Following an initial pilot project, VOT was expanded countrywide with Global Fund support in October 2016. As of 1 August 2017, the cumulative number of TB patients on VOT was 231; most patients (58%) are of active age – 26–45 years; 57% of patients work or are studying; and 50% have MDR-TB, including pre-XDR and XDR-TB. Systematic aDSM follows a set of well-defined and timed interventions over 24 months. Samples from patients enrolled on bedaquiline are sent for second-line DST (including bedaquiline) in Sweden. So far, no resistance to bedaquiline has been reported.

<table>
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<tr>
<th>Summary of preliminary results of bedaquiline and delamanid use on pre-XDR and XDR-TB patients in Belarus:</th>
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<tr>
<td>• Cohort size: 422 MDR/XDR-TB patients on new TB drugs.</td>
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<tr>
<td>• 75% converted to culture negative after 3 months.</td>
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<td>• 98% converted to culture negative after 6 months of treatment.</td>
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<td>• Four patients were “cured”.</td>
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<td>• One “failed”.</td>
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<td>• Eight were “lost to follow-up” (alcohol abuse, imprisonment and seeking work abroad are red flags, and all were adults).</td>
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<tr>
<td>• Three have died (one sudden death occurred, 3 months after stopping bedaquiline, from pulmonary embolism).</td>
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<td>• Adverse events were experienced by all patients (most commonly elevated uric acid, abnormal liver function tests, QTcF prolongation).</td>
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<tr>
<td>• 5% had serious adverse events.</td>
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**Summary of questions and comments**

- The extended use of new drugs beyond 6 months is now accepted in Belarus and is no longer questioned, even though it is not specified in the national guidelines. This acceptance could be partly explained by an earlier bad experience, as patients given linezolid through a Global Fund grant reverted 3 months after stopping the drug. Paediatricians were initially reluctant to use new drugs. Patients also trust the medical team and are willing to give their consent for extended use beyond 6 months.

- A large number of XDR-TB patients are still not receiving treatment with regimens containing new and repurposed drugs in Belarus. The reasons are not very clear, although some internal resistance to performing strict cohort event monitoring could be occurring.

**TB/HIV: Coinfection as a challenge to using new TB drugs and regimens (Dr Manfred Danilovits)**

The deadly synergy between HIV and TB has been well documented, but TB and HIV epidemics in EECA countries are fast converging. A rapid increase in the number of TB/HIV patients in most...
high-priority countries is evident, even though not all countries report all TB/HIV coinfections. It is estimated that only 61% of TB/HIV cases are being detected, the coverage with ART is 35.6% and the overall TB treatment success rate is 41%. The main risk groups are injection drug users and atypical clinical presentations. In addition, extra-pulmonary and disseminated forms of TB delay diagnosis.

TB/HIV patients face unique problems: polypharmacy is the norm (ART and treating opportunistic infections); adverse events are common; drug interactions between ART and the rifampicin group are expected; and the risk of immune reconstitution inflammatory syndrome (IRIS) can even be fatal. In addition, clinical experience with the use of new drugs and new regimens together with ART is still limited.

A summary of practical points on the clinical management of TB/HIV and the use of new drugs follows:

- All newly diagnosed TB patients in the WHO European Region should be tested for HIV and all HIV patients should be screened for TB.
- Early diagnosis of TB is paramount. Rapid diagnostic tests (Xpert MTB/RIF) should be used if available. Tests may need to be repeated more than once due to paucibacillary TB.
- ART should be offered, irrespective of CD4 count, as this will maintain a higher CD4 count.
- TB treatment is given first, followed by ART (CD4 <50: within 2 weeks. CD4 >50: within 8–12 weeks). IRIS can manifest especially with lower CD4 counts.
- A 6-month standard TB regimen is recommended for drug susceptible pulmonary TB in people living with HIV (PLHIV) who are also receiving ART. It is suggested that the continuation phase be extended by an additional 3 months if the patient is not receiving ART.
- Data on ART and MDR/XDR-TB regimens is limited. Normal doses of SLDs can be used and at least five effective drugs are included in the intensive phase.
- A shorter MDR-TB regimen of 9–12 months can be prescribed if resistance to fluoroquinolones and injectables is excluded. Linezolid and clofazimine can be used to protect a failing regimen. Drug interactions can occur, depending on the class of drugs used for ART.
- Experience on the use of bedaquiline and delamanid (alone or in combination) and ART is limited. Bedaquiline should not be used together with efavirenz due to reduction on clearance of bedaquiline in the blood. Limited evidence from interim analysis of some clinical studies suggests that bedaquiline, delamanid and linezolid are generally well tolerated but should be used with caution.

Summary of questions and comments

- Strong efforts in Estonia are showing good results, as both HIV and TB incidence rates are declining rapidly. All treatment is available free of charge, given daily and is strictly controlled. Treatment for latent TB infection among PLHIV is still resisted by some clinicians because of fear of adverse effects.

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3 A useful resource is available at [http://www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).
Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting:
Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region

- Integrated services for HIV/TB would improve compliance and make the management of drug interactions much easier. Some patients may also need methadone services.
- Anecdotal evidence suggests that the new drugs are better tolerated than para-aminosalicylic acid and pretomanid.
- The recent prequalification of GeneXpert® and HIV testing polyvalent platforms are steps in the right direction.

**Stewardship of new drugs and new regimens introduction: rGLC experience (Dr Kai Blondal)**

Impressive efforts have been made in introduction and scale-up of new drugs and new regimens. Plans and guidelines have been regularly revised and updated by WHO. Countries have received financial and technical support to revise national TB programmes (NTPs). The use of bedaquiline and delamanid has been piloted in many countries. Much progress has been made but it is not uniform across the Region and few countries have a focused plan on financing of new drugs beyond pilot projects funded by international partners. Stronger coordinated efforts are needed to develop practical country-specific plans and promote universal access to these new drugs.

The NTP is responsible for developing country-specific strategic plans and acting as the focal point for the introduction of new drugs. The readiness to scale-up may be lacking in some countries despite the fact that bedaquiline is available free of charge. In the experience of the speaker, a mix of possible reasons could be causing this problem. “Ownership” may be poor if plans were prepared by partners and the NTP managers are “invited to the feast” at the end. New drugs may be seen as the “property” of the international partners (e.g. MSF, PIH) and health systems may be unable to absorb the donations due to low human resource capacity. Not all countries have fully functional pharmacovigilance systems and companion drugs may be scarce or not affordable.

**Summary of questions and comments**

- A strong NTP is more likely to lead and “own” a strong programme and will have a more confident relationship with other international partners. GLC missions bring technical expertise but countries need to lead the health system changes necessary for the scale-up.
- Turnover within NTP staff can be an opportunity if new recruits bring new ideas and new skills.
- Capacity-building is an important component of Global Fund grants and is included in the memorandum of understanding. Some project partners may go beyond capacity-building and take over elements of the TB programme if the NTP is perceived to be too weak.
- Legal and regulatory barriers to registering new drugs are still blocking NTPs from accessing these drugs in some countries.

**Stop TB/Global Drug Facility experience: Introduction of new TB tools (Dr Maya Kavtaradze)**

The GDF facilitates access to quality assured drugs and new tools, while ensuring the lowest possible cost and uninterrupted supplies. It welcomes collaboration with active partners in the WHO European Region (e.g. KNCV and MSF) and stresses the importance of a strengthened supply chain to secure and ensure an efficient market.

New advances in the field are leading to an increased demand for products that include: new TB drugs (bedaquiline and delamanid); repurposed medicines (clofazimine, linezolid,
Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting: 
Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region

Imipenem/cilastatin; child-friendly fixed-dose formulations; and rifapentine 150 mg tablets used in short latent TB infection regimens. The GDF strategic rotating stockpile has become more efficient and lead times have been reduced to less than 3 months. The GDF has delivered and has placed orders to 12 countries in the WHO European Region for 4197 courses of bedaquiline and 688 of delamanid. It is noted that demand for the latter is slowly increasing. Kazakhstan Kyrgyzstan and Tajikistan have received new paediatric formulations while Azerbaijan and Moldova are in the planning phase.

The uptake of new TB products is still limited for a number of reasons, and a few are unique to this Region. Some examples were given from Kazakhstan, Kyrgyzstan, Tajikistan, Ukraine and Uzbekistan:

– Countries hesitate to give marketing authorization as few phase III trials are held. This serves as a reminder that the advances in this field are moving at a fast pace and experience is gradually being accumulated.
– Under-ordering for fear of retribution occurs as a result of policies that fall under “punishment for obsolete medicines”. This fact should stress the importance of having revised policy for earlier introduction and scale-up of new tools (withdrawal and destruction of obsolete medicine) and data-driven rational phase-in and phase-out transition planning with scenarios and cost estimates.
– Over-procurement has occurred, driven by suboptimal fiscal cycles and donor disbursements, or even over-ambitious targets. Orders have been cancelled and the money is not always easily reallocated. It is necessary to establish procurement frequency based on good inventory control and quantification and early warning systems. The best early warning system tool is QuanTB, which has been used successfully in nine countries in the WHO European Region.
– The resistance and treatment patterns are remarkably complex when compared with other regions. Individualized regimens with different sub-regimens are often prescribed as the effectiveness of the standard SCR is limited in some countries.

Summary of questions and comments

– Manufacturers do not recommend use of bedaquiline beyond 24 weeks and several countries are not willing to allow “off label use” even for severely ill patients. While results of phase III trials are still pending, WHO cannot make a recommendation but does not stop “off label use” in projects. The rGLC also does not have enough evidence to support or refute their use. Projects and countries are using their own protocols.
– The rGLC cooperates with the GDF but can only give an estimated “best guess” on the number of patients for drug quantification.
– The GDF can help in the preparation of the necessary documents for the registration and importation process. One time waivers for drug import are frequently used by countries. The GDF strongly advises against having two parallel drug lines of supply from donor and public acquisitions as this will confuse patients. Countries facing difficulties are encouraged to connect with others who have faced and resolved the same issues. Turkmenistan was cited as having registered all first- and second-line drugs.

*Free download available at: [http://siapsprogram.org/quantb/](http://siapsprogram.org/quantb/)*
Georgia country experience on infection control and aspects of introduction of new drugs and new treatment regimens (Dr Nestani Tuk vadze)

Georgia has made remarkable progress and was removed from the list of high MDR-TB burden countries in 2016. The rate of MDR-TB among new cases is slowly decreasing, but remains high among retreated patients (40%). Of concern is the noted increase in the number of pre-XDR and XDR-TB patients since 2009 (XDR: from 9% to 20%; any fluoroquinolone: from 12% to 36%) and the low treatment success rates (44% for MDR-TB and 21% for XDR-TB; 2013 cohort). Georgia was the first country in the WHO European Region to introduce the compassionate use of bedaquiline in 2013, and offers universal access for bedaquiline and delamanid. A total of 325 patients have been enrolled to receive these drugs. The move towards privatization of health care now offers a mix of private and public TB providers that offer full screening, diagnosis and treatment services.

Strong nationwide efforts have been made to strengthen TB infection control, stressing: timely notification; reducing diagnostic delay; high-quality treatment; ambulatory patient-centred care; and effective infection control in health-care facilities. Early diagnosis is considered crucial and the risks of hospitalization (i.e. nosocomial infection and reinfection with resistant strains) have been widely accepted. The country has shifted services away from tertiary hospitals, and the number of TB beds (8.6 per 100 000 population) is less than the estimated number projected by the TB Regional EECA Project (TB-REP) blueprint model. Significant infrastructure investments have been made. A 250-bed TB hospital was opened in 2009 in Tbilisi and is a centre of excellence in the WHO European Region. Ventilation systems for out-patient care in 30 general hospitals have been upgraded, primary health care centres renovated or newly built and a new advanced reference laboratory will open soon. Pioneering initiatives in Tbilisi are receiving Global Fund support for VOT and mobile units, taking treatment directly to the patients’ home or work place.

Georgia is at the forefront of TB research and has performed pilot studies and partnered with multinational studies on the use of new drugs, new rapid point-of-care diagnostic testing platforms and new care delivery models. These include:

- **Geno Type MTBDRplus assay:** A study on the impact of this test included a cohort of 152 patients receiving treatment at the National Centre for Tuberculosis and Lung Diseases in Tbilisi, Georgia. The pre- and post-arms of the study showed significant reductions in the delay before starting an MDR-TB treatment regimen and in the mean number of days spent by MDR-TB patients in the “drug-susceptible” wing of the TB ward.

- **Xpert MTB/RIF Ultra Trial:** Georgia enrolled 313 patients in this international multicentre trial, which was led by FIND. Results showed that RIF Ultra had better sensitivity but less specificity. A WHO technical expert consultation recommends that the Ultra assay replace Xpert MTB/RIF assay in all settings.

- **Cepheid GeneXpert® Omni/Ultra Trial:** Primary health care facilities in Georgia are participating in this prospective multicentre trial. This is a promising point-of-care test for earlier diagnosis at peripheral centres as the system is robust, cartridges are compatible with earlier models and it is more economical – taking one sample at a time.

- **TB drug multicentre clinical trials:** Georgia is actively contributing to new drug and new regimen development and is taking part in a number of phase III trials (STAND, NiX-TB, STREAM).
Summary of questions and comments

- Some countries still rely on the capacity of projects that are run by international partners for active pharmacovigilance, but awareness is increasing. Belarus was cited as having advanced well in this area. Kazakhstan is planning to move from passive event reporting by doctors to aDSM.
- A VOT pilot was started in 2016 with 50 MDR/XDR-TB patients in Tbilisi and is now being extended to other regions. Results so far show no missed doses and a number of patients have completed treatment. The main problem is meeting the patients’ preference for taking the drugs at night.

European Tuberculosis Laboratory Initiative (ELI) and the ELI diagnostic algorithm (Dr Soudeh Ehsani)

The laboratory network and DST coverage in the Region are strengthening, however the targets set in the Tuberculosis Action Plan for the WHO European Region 2016–2020 may not be reached unless the MDR-TB case detection rate improves and quality-assured second-line DST is scaled up more rapidly. ELI was launched in 2012, with strong support from USAID. The new Core Group members for 2016–2018 have set three goals: to further strengthen the capacity to detect MDR-TB, to support the appropriate use of WHO recommended rapid molecular testing, and to assure laboratory standards for quality, maintenance and biosafety.

A regional TB laboratory diagnostic algorithm was launched on World TB Day 2017 in both English and Russian after extensive consultation and pilot testing. This resource facilitates early diagnosis, gives specific advice dealing with discordant results and provides a systematic plan for follow-up of both drug-sensitive and MDR-TB patients. Phenotypic methods of DST for both first- and second-line drugs remain the gold standard; however, genotypic (molecular) methods have several advantages: they are very practical, easier to use, give faster results, use standardized methods, have high through-put and have lower biosafety requirements.

The WHO preferred front-line rapid molecular tests are LPAs and GeneXpert® MTB/RIF. These are recommended for the initial diagnosis of TB and RR-TB (Xpert MTB/RIF). Second-line LPAs are preferred for detecting resistance to second-line injectable drugs and fluoroquinolones. First-line LPAs have very high sensitivity (exceeding 90%) and specificity (exceeding 99%) on smear-positive and culture-positive sputum samples. Second-line LPAs can detect non-specific resistance to fluoroquinolones and injectable second-line drugs (~ 86% of cases) and XDR-TB (~ 69% of cases).

Summary of questions and comments

- The laboratory infrastructure in the WHO European Region is still heavily based on the older techniques and needs to adapt to new methods. However, old techniques still have to be used in tandem while the understanding and expertise of molecular techniques advance. This entails extra costs and workloads for laboratory systems and WHO will issue new guidelines on this.
- DST for redundant drugs, such as ofloxacin, is still reported in many countries. The reproducibility of cycloserine sensitivity testing is very poor. Laboratories need to give a bolder message to clinicians and also be involved in clinical decisions to adapt regimens
according to DST. New techniques that do not detect MDR-TB such as loop-mediated isothermal amplification (TB-LAMP) are not useful in this Region.

– Discordant results between old and new methods need to be interpreted in the clinical context of each patient. Whole genomic (molecular) sequencing is not widely available in the Region and is not standardized, as different labs use different algorithms and thresholds.

– It is possible that some clinicians may resist new diagnostic methods due to incomplete understanding. The ELI algorithm aims to educate, and ensure the scientific rigor of these methods. The reduction of pay benefits due to lower biohazard risks is a potential source of resistance by laboratory technicians in some countries.

Overview of TB challenges in the EECA region: Addressing challenges through improved collaboration (Dr Artashes Mirzoyan)

The EECA region is challenged by the highest levels of MDR-TB globally and a legacy of care based on expensive hospitalization. An alarming spread of HIV infection is occurring among injecting drug users, and coinfected TB/HIV patients in EECA countries are already showing poorer treatment outcomes, even for drug-sensitive TB. Although public funding for TB services is significant (66% of total spending), MDR-TB services rely heavily on the Global Fund (61% of all allocations), with 66% of EECA countries relying on external funding for second-line drugs, 58% for DST and 94% for GeneXpert® testing.

EECA nations are no longer regarded as low-income countries by the Global Fund, and all will experience a significant reduction (more than 50% in most instances) in the next allocation round (2018–2020). Any subsequent investment will target options for maximum impact on the new threat of TB/HIV in the region, and it is clear that the vertical systems delivering care need to be integrated. EECA countries in general have been unable to absorb the total grant allocations, and the average burn-out rate is estimated to be 40–65%. This is a lost opportunity, as strict rules on unspent amounts apply. The reasons for low spending can be very country-specific and the situations in Kyrgyzstan, Tajikistan and Uzbekistan were described. General reasons include: depreciation of local currencies; low rates of actual demand for the drugs (because of low MDR-TB case detection, common patient default and poor data); and legislative barriers to registration of new drugs (thus not accessible from the GDF).

Most governments are not living up to their commitment to increase their share of spending to smooth the transition from Global Fund support. The Global Fund seeks the assistance of the rGLC and other partners to address the causes of low case detection and the barriers to the short MDR-TB treatment regimens. The rGLC could also follow up on the mission recommendations made to countries to see that they are implemented, and push for strengthened health systems.

Summary of questions and comments

– The retreat of the Global Fund is causing a lot of uncertainty in a region that has the highest burden of MDR and XDR-TB. Treating affected patients is very difficult and, in many instances, is still not fully understood by local clinicians. Furthermore, XDR-TB is a new phenomenon and needs closer study. Stronger advocacy at all levels, including by WHO, is needed to lead the Global Fund to reconsider its position.
The majority of Global Fund decisions are based on reports from other partners, and rGLC country mission reports are a very important resource. The quality of the data that is used by the Global Fund for target setting is the subject of some debate. rGLC consultants observe that the reality on the ground can be different from official WHO data. A case in point is the difference between the number of estimated and actual XDR-TB patients in some countries. It was suggested that the Global Fund should consider using updated epidemiological reviews issued by the WHO Regional Office for Europe (such as WHO surveillance response monitoring reports) for its operational planning.

While the Global Fund is ready to support countries, the lack of implementation of mission recommendations leaves a negative impact on new grant applications. Strong grant applications also include a civil society organization component. rGLC members and the GLC Secretariat have to explore more effective and systematic ways to ensure follow-up on country missions.

Diagnostic techniques are changing rapidly and there is no systematic approach to reviewing the standards and quality of laboratories. Linking the rGLC with ELI can be useful.

Drugs that are procured with Global Fund grant support need to be physically present in the receiving country before the expiry of the current grant. The value of a drug consignment which is not received in time can be deducted from future allocations.

The influx of migrants in the region is a new challenge. Health care for this group of patients is often not covered by NTP finances and thus services offered can be lacking or limited.
Face-to-face meeting on 27 July 2017

Dr Masoud Dara welcomed rGLC members and new participants to the meeting and thanked them for their support in the implementation of the Tuberculosis Action Plan for the WHO European Region 2016–2020. Dr Andrei Maryandyshev, as chair of the meeting, presented the agenda for the day. He reminded participants that rGLC/Europe was established in 2011 and was the first of the regional Green Light Committees to be appointed. Dr Ogtay Gozalov reminded participants of the recommendations and action points from the rGLC meeting of the previous year. He also announced that rGLC/Europe meetings and reports will no longer remain confidential.

The ownership and access to mission reports was raised immediately and the following points were made:

- The ownership of the technical advisory and monitoring mission reports was discussed at length during a Global GLC meeting that included all six regional committees. Regions have a different understanding on this issue. No final position was adopted.
- The WHO Regional Office for Europe, as rGLC/Europe Secretariat, appreciates that countries own the data and the mission reports. Countries who have published their full report online have seen very positive results from international donors (e.g. Romania). However, as the Global Fund places transparency as a condition for funding missions, a summary of rGLC/Europe mission reports will be available on the rGLC web page that is hosted on the Regional Office website.

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

European TB Research Initiative (ERI-TB, Dr Andrei Dadu)

ERI-TB was launched in November 2016 as one of the key milestones in the TB Action Plan for the WHO European Region 2016–2020, with the specific mission to advance TB-related research in the Region. A Core Group of 15 experts from diverse backgrounds was established and the chair nominated. Efforts are ongoing to extend the network. The Core Group have met twice and meeting reports are openly shared on the ERI-TB page on the Regional Office website. A Delphi consultation among the Core Group members was conducted in an effort to collate a list of specific research questions that are important for the Region. A list of 85 research questions was produced that cover three general thematic areas: epidemiology, new discoveries in basic science and new tools, and operational research. The list will be shared through an online country consultation among NTP managers, and each will identify and set their own national priorities. The final results will be included in a policy paper on priority research for the Region.

Summary of questions and comments

- The Regional Office is organizing meetings in Ukraine and Estonia to increase capacity-building in data analysis and data interpretation as well as in operational research. Countries can ask the Regional Office for support to conduct more TB research.
- Little interest and funding for TB research is forthcoming from the private sector. Other fields, such as HIV attract more attention. It is expected that the Moscow Global Ministerial Conference that is due in November 2017 will leave a positive mark on global and regional TB research efforts.
TB-REP regional project (Dr Masoud Dara)

TB-REP is a 3-year project supported by the Global Fund and covers 11 EECA high-burden countries in the WHO European Region. The principal recipient of the grant is the Centre for Health Policies and Studies (Ukraine) and includes international and national civil society organizations as partners. The project seeks to increase political commitment and improve treatment outcomes, while reducing unnecessary hospitalization. It advocates for aligning health financing towards people-centred TB models of care. A “Blueprint for EECA Countries” was launched in June 2017, and is a data-driven tool that can plan ambulatory care models to reduce unnecessary and lengthy hospital admissions. The next edition will include patient reviews on the quality of care. Country road maps for health system strengthening are being developed and the WHO Barcelona course on “Health Systems Strengthening for Improved TB Prevention and Care” has become an important and popular capacity-building resource. A breakfast meeting is planned with the ministers of health of TB-REP countries during the 67th session of the WHO Regional Committee for Europe, in September 2017, to discuss progress and challenges. The champion countries will present their experience and the blueprint will be communicated to a wider audience during the Moscow Global Ministerial Conference in November 2017.

Summary of questions and comments

– Some countries still depend heavily on the Global Fund to deliver treatment and care for MDR/XDR-TB and they will struggle when the Global Fund withdraws its support. This increases the value of the blueprint. rGLC consultants are encouraged to refer to the blueprint during country missions.
– Decentralization of health services is seen by some health-care workers as a threat to their livelihood and can become a sensitive issue to locally elected politicians. The needs of all health-care workers are important and must be addressed for task shifts and a smooth transition.
– TB is no longer popular as a medical speciality. Georgia was cited as an example, where the average age of chest physicians is 58 years, and peripheral clinics lack TB specialists. TB-REP is also advising some countries on this issue.
– Although countries have ratified conventions on human rights and the right to health, some still have legislation that is not compliant with basic patient rights (e.g. allowing involuntary isolation).
– The use of new technology to actively monitor patient compliance and drug safety is spreading in the Region. The possibility of WHO organizing a meeting to document and map good practices on eHealth in the Region was raised.

Panel discussion 1. How can the rGLC/Europe do things differently and do more in country support provision?
Chair: Dr Andrei Maryandyshev
Panel: Dr Kai Blondal, Dr Ogtay Gozalov, Dr Andrei Mosneaga, Dr Askar Yedilbayev

5 Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Republic of Moldova, Tajikistan, Turkmenistan, Ukraine and Uzbekistan
Practical insights: The rGLC is a technical advisory group, has no authority to implement national TB plans in countries and has to recognize its limitations. Any further scale-up requires health system strengthening that is beyond the remit of the rGLC. However, rGLC missions are very useful to identify basic service gaps, such as insufficient electrocardiogram (ECG) machines, blood electrolyte measurement and audiogram testing.

Leverage: Leverage is important but reflects funding capability. While WHO and other international agencies have strong political influence, rGLC consultants are respected for their technical expertise. NTP managers should be the first line of contact during rGLC missions, and seeking more direct contact with ministry of health officials can improve outcomes. The active support of WHO is needed for this to happen. rGLC recommendations that are consistent and relevant to the needs of the country are key to advancing the expert power of the rGLC in the Region.

Addressing the retreat of the Global Fund: The retreat of Global Fund and other donors in the Region is a problem. Government funding will not be sufficient to cover health-care costs for the high burden of drug-resistant TB, which is now compounded with the alarming increase in HIV/TB comorbidity. Funding for capacity-building (such as paying for translators) and outreach in the community is already very scarce. New funding is urgently needed from new partners (the United Kingdom’s Department for International Development (DFID) was mentioned as one example). A strong case should be made to the Executive Board of the Global Fund to review its position, stressing the suffering that will result among the most marginalized population groups.

Increasing efficiency: Better planning, avoiding duplication and sharing success stories through better communication allows better use of resources. This includes: communication between the rGLC and stakeholders (including WHO country offices alerting ministries of health of upcoming visits) and partners (such as MSF, KNCV, USAID projects and civil society organizations); performing short training updates for key staff; and sharing best practices to overcome local barriers (e.g. local procurement of quality second-line drugs and avoiding drugs stock-outs). The need for the rGLC Secretariat to enhance human resources is noted.

Targeted missions: rGLC missions need to be targeted to the specific needs of the host country. Consultants should call on other experts to address areas which go beyond their technical speciality, such as technical experts for laboratory services (e.g. ELI), as well as legislative and advocacy experts (e.g. TB-REP) to support transition from in-hospital to ambulatory and community modes of care.

Positive labelling: The title used to describe the purpose of visits should emphasize more the technical advisory, communicating and coordinating roles of the rGLC. The use of the label “monitoring missions” may be interpreted negatively and put country counterparts on the defensive.

Revised monitoring tool: The reporting tool does not reflect the scope of rGLC missions. The last revision was made in 2011. Mission reports are too long and do not focus on the specific needs of the countries. The revised tool would include: an executive summary with key recommendations;
recommendations (smart and graded recommendations so that implementation can be measured, possibly using a traffic light system); timed actions; a summary PowerPoint presentation (with a maximum of eight slides); key performance indicators (including uptake and coverage of new diagnostics, new drugs and new regimens; and progress reports between missions, which are essential for Global Fund review); and an epidemiological data table to be completed by the NTP manager. Data entry is often incomplete and national and WHO published data may not agree. Official WHO data should be used, and if important discrepancies are noted, the Regional Office should be alerted.

Language: The language of published reports is a barrier in non-English speaking countries. Translation is costly and takes a long time. Translation costs may be covered by the Global Fund under capacity-building activities. Knowledge of the local language is very helpful during the missions. Country action plans need to keep up with and reflect new and updated WHO guidelines. WHO guidelines can be translated into other languages under the Creative Commons licence.6

rGLC consultant pool: The TB field is no longer static as new drugs, new regimens and new diagnostic methods become available. New junior rGLC consultants are mentored by senior experts and should be confident in disseminating new knowledge among hesitant national counterparts.

Assisting the GDF: The rGLC can relay information for drug quantification and forecasting in the Region. The WHO European Region is unique because a wide range of drug regimens are prescribed. It is possible that data on consumption and future needs of specific drugs and regimens can be collected and shared at the end of country missions.

Avoiding conflicts of interest: The increasing interest and engagement of stakeholders and private partners is welcome; however, conflicts of interest must be avoided. Mission operations must be completely independent and free of any external interference.

Panel discussion 2. What are the main pitfalls in implementation of the national TB action plans?
Chair: Dr Andrei Maryandyshev
Panel: Dr Manfred Danilovits, Dr Gunta Dravniece, Dr Elmira Gurbanova, Dr Ogtay Gozalov

Perceived ownership: In some cases, the national TB action plans that are designed by external consultants may appear polished, and can end up “just for show to the Global Fund” if they do not reflect the actual needs of the country. They should be operational and not political instruments. Strong national plans involve many stakeholders and are approved by government decree, thus

6 Some rights reserved. A translation should add the following disclaimer along with the suggested citation: “This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition”.

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rendering implementation mandatory in former-Soviet countries (Kazakhstan was cited as an example of a strong TB national plan leading to the introduction of new drugs.) The preparation of a national action plan is a valuable experience in itself.

**Assigned responsibility:** Ministries of health have the final responsibility to implement the national TB action plan through the NTP. Strong political commitment ensures more effective implementation. WHO offers technical advice in preparing a clear implementation plan. The local Country Coordinating Mechanism can also assist countries in their applications to the Global Fund, but the strength of these national committees may vary.

**Plans covering many years:** Action plans need to be reviewed both for technical and financial aspects, so that guidelines are up to date. Clear milestones are set for the introduction of new drugs and diagnostic tools. Transition planning for phased reduced Global Fund support is very important and often lacking. Annexes can be added with operational up-dates. Separate sections can inform on phasing in new drugs and phasing out of obsolete drugs.

**Unrealistic targets:** Targets should be achievable and address country priorities. Very long-term targets are best avoided. An embedded mid-term evaluation ensures that progress is monitored and reported (Georgia was cited as performing mandatory mid-term evaluation with good results). Success stories need to be shared more widely between countries in the Region.

**Lack of resources reflecting poor political commitment:** National action plans are themselves non-binding and may serve purely as instruments to qualify countries for Global Fund grants. Governments may not approve plans in their totality because of competing interests, leaving many activities financially unsupported. A stronger political commitment is needed to ensure sufficient resources are available through domestic financing as the Global Fund pulls out of the Region. Sharing best practices during high-level ministerial meetings can serve to convince ministers and bring political support.

**Reliable measurement of drug resistance:** Multidrug resistance, especially XDR-TB, appears to be increasing and is partly a reflection of improved case finding. Antimicrobial resistance needs to be reliably measured but is inherently an inexact science as: case definitions have only recently been established; correlating phenotypic with molecular diagnostic methods is still uncertain; optimal drug dosages are under revision; and the quality of DST is variable.

**Insufficient access to new drugs:** Slow uptake of bedaquiline still occurs because of uncertainty surrounding procurement procedures (e.g. whether orders should be added on top of the government procured background regimen). Only a small percentage of eligible patients receive proper treatment in some countries (e.g. it is estimated that in Belarus only 20% of the eligible cohort of patients are receiving good-quality treatment from the Global Fund).

**Unaddressed country-specific challenges:** Comorbidities affect treatment outcomes and may not be fully addressed. The spread of TB in the Region among those with HIV and among injection drug users is increasingly recognized. Alcohol abuse is a very common problem but remains poorly studied and mostly ignored. A case for more funded research in these areas needs to be made.
Panel discussion 3. What is the role of partners and civil society in the implementation of the Tuberculosis Action Plan for the WHO European Region 2016–2020?

Chair: Dr Andrei Maryandyshev
Panel: Dr Sevim Ahmedov, Dr Sergiy Filippovych, Dr Ogtay Gozalov, Dr Andrei Maryandyshev

**Beyond advocacy:** Civil society organizations (CSOs) add value and support all three pillars of the TB Action Plan 2016–2020. They are uniquely placed to reach vulnerable populations through social networking and provide a bridge between hard to reach groups and health services. For example, peer support in Ukraine has resulted in a doubling of positive treatment outcomes among MDR-TB patients.

**Supporting people-centred care:** CSOs in countries have worked closely with TB-REP, which has just launched the first edition of the blueprint for a people-centred model of TB care. This work focuses on ambulatory treatment, strengthening primary health care services and integrating health systems in 11 EECA countries. CSOs are also working closely on country-specific road maps to support the best use of available resources for TB care.

**Protecting patients’ rights:** TB is a social disease with clinical aspects. Stigma and discrimination are barriers that interfere with seeking care and completing treatment. Patients can lose their parental rights or be compelled into involuntary hospitalization. Some may even be abandoned by their family.

**Strengthening political commitment:** The TB Caucus is a formal coalition of parliamentarians and is putting TB on the political agenda. A strong commitment is expected from the upcoming Moscow Global Ministerial Conference in 2017 and the United Nations high-level meeting on TB in 2018.

**Mutual support:** CSOs can prove extremely useful to rGLC missions especially in crisis situations (e.g. CSO partners removed barriers during an rGLC mission in Kyrgyzstan). Although CSOs have their own agenda it is critical for the rGLC to seek their cooperation as rGLC missions are short and infrequent. TB-REP members in countries can be highly influential and can be useful during rGLC missions. rGLC consultants can contribute to capacity-building among CSOs by inviting them for training workshops in countries and also sharing best practices.

**Strengthening demand:** Grassroots activism has been a strong driver in the fight against HIV, but TB activism is not as strong. Access to new, high-quality drugs and new diagnostics can be increased if a stronger demand is created. This can be led and driven by civil society and patient groups. On the other hand, CSOs must educate patients and emphasize the reality that new drugs will become useless if they are not used responsibly.
Conclusions

- A scale-up of new drugs and new regimens is evident in the WHO European Region, thanks to the collaboration and support of Member States and international partners that include of the Global Fund, the GDF, the endTB Project, MSF, PIH and USAID.
- The retreat of the Global Fund from the Region is a cause for great concern and uncertainty is gripping many NTPs. This disengagement is occurring in spite of a very high burden of MDR-TB. The recent emergence of XDR-TB strains, a rapid increase in the numbers of people coinfected with HIV/TB, as well as unplanned mass migrations across international borders are all unforeseen but significant epidemiological trends and threats.
- Access to first- and second-line DST in EECA countries has improved significantly and a high diversity of unique mycobacterial drug resistance patterns has been revealed. This has direct implications on the need for highly individualized treatment regimens and renders drug quantification and forecasting more difficult.
- EECA countries are at the forefront of the rapid advances that are occurring in the field, and are participating in TB research in collaboration with international partners. Results from early prospective studies on the “off label use” of bedaquiline and delamanid look very promising. The response to the treatment, especially among severely ill patients, can be dramatic and both drugs seem to be well tolerated.
- The technical contribution of the rGLC to countries is highly relevant and the impact of missions can be strengthened further. More emphasis could be placed on the technical and cooperation aspects, as opposed to “monitoring missions”. Mission reports need to be redesigned and improved. CSOs are important stakeholders and are also important partners.

Recommendations of the rGLC/Europe face-to-face meeting, 27 July 2017

Recommendations for WHO

- Use the momentum to advocate for increased political commitment to TB control during the ministerial meeting in 2017. WHO/Europe: prepare bullet points for the Regional Director to use in meetings with ministers attending the conference.
- Continue the work of the Joint Tuberculosis, HIV and viral hepatitis (JTH) 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. TB-REP can facilitate these processes and share good practice among countries. Share reports with DHS&PH and invite them to follow-up calls on implementation of the rGLC/Europe recommendations.
- The rGLC/Europe Secretariat in collaboration with WHO country representatives and country officers: communicate with the ministry of health and partners in countries ahead of rGLC missions, and share the terms of reference to ensure successful rGLC and other technical assistance.
Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting: Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region

- Discuss with NTP managers the possible ways in which the ministry of health 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.
- Consider searching for additional funding to enlarge the pool of rGLC consultants.
- Consider searching for additional funding to enlarge the rGLC Europe Secretariat.
- 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.
- Agree on more focused terms of reference with NTPs and the ministry of health, 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.
- Encourage face-to-face discussions with key European Region governments and agencies to encourage TB-specific funding in the Region.
- Encourage countries and provide technical assistance on updating the national action plans, and advise on substantial increases in government funding.
- Pursue financial gap analysis during the financial sustainability related missions. Ask the ministry of health on the fin gaps for TB in the countries. Invite the Global Fund to a workshop on financial analysis.
- 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 GDF.

Recommendations for partners
- Look into the available financing on the ground and help the NTP to pull the available funding together to ensure sustainability.
- Consider sharing partner reports or other relevant data with WHO (rGLC).
- Contribute to the dissemination of the recent WHO recommendations and guidelines in the countries.
- Advocate for mobilizing new funds and new donors internationally.
Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting:
Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region

Supporting documents


# Annex 1: Programme

**Workshop, 25 July 2017**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00–09:30</td>
<td>Introduction</td>
<td>Dr Masoud Dara&lt;br&gt;Opening, adoption of agenda and programme&lt;br&gt;Briefing on background, purpose and expected outcomes</td>
</tr>
<tr>
<td>09:30–10:00</td>
<td>Session 1</td>
<td>Dr Ogtay Gozalov&lt;br&gt;Latest updates: WHO’s Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017)</td>
</tr>
<tr>
<td>10:00–10:30</td>
<td>Session 2</td>
<td>Dr Gunta Dravniece, KNCV&lt;br&gt;Challenge TB experience in programmatic introduction of new drugs and shorter DR-TB treatment regimen in WHO Euro region</td>
</tr>
<tr>
<td>10:55–11:40</td>
<td>Session 3</td>
<td>Dr Jay Achar, MSF (via WebEx)&lt;br&gt;MSF experience on introduction of the new drugs: clinical aspects and challenges of the new drugs (bedaquiline and delamanid) introduction</td>
</tr>
<tr>
<td>11:40–12:25</td>
<td>Session 4</td>
<td>Dr Askar Yedilbayev&lt;br&gt;PIH experience on introduction of the new drugs: clinical aspects of the new drugs (bedaquiline and delamanid) introduction</td>
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<tr>
<td>13:40–14:25</td>
<td>Session 5</td>
<td>Dr Manfred Danilovits&lt;br&gt;TB/HIV as challenge for introduction of new drugs/new regimens</td>
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<tr>
<td>14:25–15:10</td>
<td>Session 6</td>
<td>Dr Kai Blondal&lt;br&gt;Stewardship of new drugs and new regimens introduction: GLC expert experience</td>
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<tr>
<td>15:25–16:10</td>
<td>Session 7</td>
<td>Dr Maya Kavtaradze&lt;br&gt;GDF experience: drugs management aspects of new drugs introduction</td>
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<tr>
<td>16:10–16:55</td>
<td>Session 8</td>
<td>Dr Alena Skrahina&lt;br&gt;Belarus: country experience on introduction of new drugs and new treatment regimens</td>
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**Workshop, 26 July 2017**
### Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting:
**Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Description</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00–09:45</td>
<td><strong>Session 9</strong> Georgia: country experience on infection control aspects of introduction of new drugs and new treatment regimens</td>
<td>Dr Nestani Tukvadze</td>
</tr>
<tr>
<td>09:45–10:30</td>
<td><strong>Session 10</strong> Lab aspects of the new treatment introduction, including diagnostic algorithm</td>
<td>Dr Soudeh Ehsani</td>
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</tbody>
</table>
| 10:55–11:55 | **Session 11** Donors perspectives: update on USG drugs donation programmes  
|              | Donors perspectives: updates from Global Fund support                                                  | Dr Sevim Ahmedov  
|              | Dr Artashes Mirzoyan                                                                                  |                                                 |
| 11:55–12:10 | **Session 12** Lessons learned from the workshop and experience exchange                              | Dr Ogtay Gozalov                                |
| 12:10–12:40 | **Closure of the workshop**                                                                             | Dr Masoud Dara                                 |

**Face-to-face meeting, 27 July 2017**

<table>
<thead>
<tr>
<th>Time</th>
<th>Description</th>
<th>Speaker(s)</th>
</tr>
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</table>
| 09:00–09:30 | **Introduction**  
|              | 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**       | Dr Ogtay Gozalov                                
|              | Updates from the European Research Initiative  
|              | Updates on TB-REP regional project                                                                    | Dr Andrei Dadu  
|              | Dr Masoud Dara                                                                                        |                                                 |
| 11:00–12:00 | **Panel discussion** How rGLC/Europe could do differently and do more in country support provision     | Dr Andrei Mosneaga                              
|              | Dr Kai Blondal                                                                                        | Dr Askar Yedilbayev                             |
| 12:00–13:00 | **Panel discussion** What are the main pitfalls on implementation of the national TB Action plans      | Dr Elmira Gurbanova                             
|              | Dr Gunta Dravniece                                                                                    | Dr Manfred Danilovits                           |
| 14:00–15:00 | **Panel discussion** Role and place of the partners and civil society in the                          | Dr Andrei Maryandyshev                          |
Regional Green Light Committee for the WHO European Region workshop and face-to-face meeting:
Introduction of new medicines for the treatment of drug-resistant tuberculosis in the WHO European Region

Implementation of the European TB Action Plan. Dr Sergiy Filippovych
Dr Sevim Ahmedov

15:15–16:00 Panel discussion
Development of recommendations to WHO and rGLC/Europe Dr Askar Yedilbayev
Dr Kai Blondal
Dr Andrei Mosneaga

17:00–17:30 Closure of the meeting Dr Masoud Dara
Annex 2: List of participants

rGLC/Europe members
Dr Andrei Maryandyshev, Chair rGLC/Europe
Dr Manfred Danilovits
Dr Gunta Dravniece
Dr Askar Yedilbayev
Dr Andrei Mosneaga
Dr Kai Blondal
Dr Elmira Gurbanova
Dr Sergiy Filippovych
Dr Jay Achar, Médecins Sans Frontières (MSF)
(via WebEx)

rGLC/Europe consultants/supporters leading introduction of new medicines and new treatment regimens
Natavan Alikhanova, Azerbaijan
Armen Hayrapetyan, Armenia
Alena Skrahina, Belarus
Giorgi Kuchukhidze, Georgia
Nana Kiria, Georgia
Yelena Arbuzova, Kazakhstan
Gulnora Mussabekova, Kazakhstan
Bakyt Myrzaliev, Kyrgyzstan
Olga Pavlova, Ukraine
Iana Terleieva, Ukraine
Dilrabo Ulmasova, Uzbekistan
Asgar Ismaylov, MSF

European TB Laboratory Initiative representative, Core Group Secretariat and external laboratory consultant
Francis Drobniewski

Global Drugs Facility
Maya Kavtaradze

The Global Fund
Artashes Mirzoyan
Sandra Irbe
David Kokiashvili
Ganna Bolokhovets

United States Agency for International Development (USAID)
Sevim Ahmedov

WHO Regional Office for Europe
Dr Andrei Dadu
Ms Anne-Brigitte Gradman
Dr Ann Galea, reporter
Dr Nestani Tukvadze
Dr Martin van den Boom
Dr Masoud Dara
Dr Ogtay Gozalov
Dr Soudhe Ehsani
Ms Tatsiana Burzhynskaya
Ms Vittoria Gemelli

WHO Europe Regional Collaborating Committee (RCC TB) representative
Jonathan Stillo, TB Europe Coalition

WHO headquarters
Dr Malgosia Grzemska