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Regional Green Light Committee for the WHO European Region face-to-face meeting

Copenhagen, Denmark, 4–5 August 2016

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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 4–5 August 2016. The specific objectives were to update and align regional policies on new treatment regimens and the use of new drugs and diagnostic techniques according to WHO global recommendations. Invitees included members of rGLC/Europe and representatives from the WHO Regional Collaborating Committee, the European TB laboratory initiative, the Global Drugs Facility, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the United States Agency for International Development. Speakers from WHO headquarters also attended. Participants presented recommendations for WHO and partners and defined action points for the rGLC/Europe.

Keywords

TUBERCULOSIS, MULTI DRUGS-RESISTANT
EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS
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Acronyms

Bdq	bedaquiline
Dlm	delamanid
DST	drug-sensitivity testing
GDF	Global Drugs Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
MDR-TB	multidrug-resistant tuberculosis
M/XDR-TB	multidrug and extensively drug-resistant tuberculosis
NTP	national tuberculosis programme
PMDT	programmatic management of drug-resistant tuberculosis
rGLC/Europe	regional Green Light Committee for the WHO European Region
TB	tuberculosis
USAID	United States Agency for International Development
XDR-TB	extensively drug-resistant tuberculosis

Introduction

The regional Green Light Committee for the WHO European Region (rGLC/Europe) was established in response to the high burden of multidrug-resistant tuberculosis (MDR-TB) in the Region. It provides technical assistance and advisory support to the WHO Regional Office for Europe, countries and partners in developing, revising and implementing national programmatic management of drug-resistant TB (PMDT) plans. The rGLC/Europe is hosted by the Regional Office.

A face-to-face meeting of rGLC/Europe was held in Copenhagen, Denmark, on 4–5 August 2016. The specific objectives were to update and align regional policies on the use of new anti-TB and repurposed drugs, recent chemotherapeutic regimens, and new technologies and diagnostic techniques according to WHO global recommendations.

The meeting was webcast via WebEx and national TB programme (NTP) managers in countries of the Region were encouraged to join. It was opened by Masoud Dara of the Regional Office and chaired by Dr Andrei Mariandyshev, chair of rGLC/Europe. No conflicts of interest were declared by participants.

This report summarizes the discussions, conclusions and recommendations arising from sessions and highlights the action points moving forward. The programme is shown in Annex 1 and participants in Annex 2. The revised pre-rGLC mission form is provided as Annex 3.

Main discussions and conclusions

The rGLC/Europe and United States Agency for International Development (USAID): in support of the End TB Strategy and progress report

The rGLC/Europe has actively supported the implementation of the End TB Strategy and the TB action plan for the WHO European Region 2016–2020, in line with overarching goals set by the Health 2020 European policy framework. The rGLC/Europe provides a key platform for assisting countries to provide high-quality PMDT in the Region and helping them successfully to obtain grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

The TB action plan for the Region 2016–2020 sets three ambitious targets: reducing mortality from TB by 35%; reducing TB incidence by 25%; and achieving a 75% treatment success rate among MDR-TB patient cohorts. The last target is key to enabling the first two to be met. Twenty-five rGLC/Europe missions in support of these goals have been completed since 2015. All national strategic plans in the Region have been updated and have been instrumental in the success of grant applications to GFATM. Four NTP reviews have recently been integrated with rGLC/Europe missions, with consultants in Ukraine and Uzbekistan providing enormous support at short notice.

The scaling-up of new and repurposed TB drugs and diagnostic techniques is posing novel challenges. Some countries are hesitant about adopting these innovations, demanding stronger scientific evidence and proof that they provide added value over current practice. WHO continues to support these countries to introduce new drugs and assure smooth transitions on introduction of short-treatment regimens.

The clearly expressed commitment of the government of the United States of America to address the challenges posed by MDR-TB and extensively drug-resistant TB (XDR-TB) at home and in high-burden countries is complemented by rGLC/Europe support and the national action plan for combating MDR-TB. The plan describes a set of short-, medium- and long-term targets and expected outcomes, such as ensuring that at least 50% of MDR-TB patients in countries with the highest burden will receive treatment by 2020. It emphasizes patient-centred care and prevention approaches, and bold policies and supportive systems that are complemented by intensified efforts in research and innovation. Specific activities include strengthening TB laboratory networks, ensuring rigorous surveillance and monitoring, expanding MDR-TB treatment capacity, and improving the availability and affordability of quality-assured second-line drugs globally. Strengthened collaboration between USAID and the rGLC/Europe is anticipated as two countries in the Region (Kazakhstan and Ukraine) are on the high-priority country list. Six countries in the Region have already received support through the bedaquiline (Bdq) donation programme.[1]

Most of the previous recommendations made to the rGLC/Europe are still being implemented. Steady improvements in MDR-TB detection rates and access to treatment have been attained and

[1] The marked variation reported in the proportions of Bdq ordered by countries in the Region versus the estimated need (Belarus 84%, Georgia 52%, Kazakhstan 16%, Kyrgyzstan 8%, Tajikistan 23% and Uzbekistan 10%) is noted.

health financing strategies have improved. Progress is inconsistent across the Region, however: consequently, the burden of MDR-TB cases in some countries remains high. Over 23% of new pulmonary TB cases in non-European Union and European Economic Area countries had MDR-TB, implying ongoing transmission in the community; nosocomial transmission is also problematic. Persistently high hospitalization rates are still observed in some countries due to perverse institutional financial incentives and the capacity to treat multidrug and extensively drug-resistant TB (M/XDR-TB) cases is insufficient in some countries because of barriers to accessing second-line drugs. The proportion of MDR-TB in previously treated patients has nevertheless stabilized over the past five years.

Discussion

- The need for a mechanism to enable systematic follow up of country progress after rGLC/Europe missions was raised. It is essential that recommendations made by consultants in mission reports are practical, implementable, followed up actively and implemented effectively.
- Updating national treatment guidelines to follow new WHO policies is problematic if countries have not registered the new drugs. Specific training from rGLC/Europe consultants on scaling-up new drugs and diagnostic techniques would be useful.
- Scaling-up of access to new medicines is inconsistent across the Region. Registration of new anti-TB drugs could be accelerated if countries that are doing well in a particular area were encouraged to share their experiences. The recent availability of clofazimine and linezolid in Uzbekistan was noted during the discussion.
- Rapid changes and advances in the management of TB patients, such as the initiation of ambulatory (outpatient)-based treatment, introduction of Bdq, delamanid (Dlm) and other new and reprofiled medicines, and development of short-course drug-resistant TB treatment are welcome. Full consideration should be given to mycobacterial resistance patterns in the Region, with treatments adapted to reflect the resistance pattern.
- The TB regional eastern Europe and central Asia project can assist countries to change their model of care towards a more patient-centred approach: countries with stronger NTPs have lower hospitalization rates.
- Data surrounding nosocomial transmission and transmission in the community need to be strengthened and further analysed.
- NTP members and civil society groups are not always involved during rGLC/Europe joint missions and information on planned activities and mission reports is not easily available. WHO can make summaries of the missions publicly available, but enabling access to full reports is up to individual Member States.

New diagnostic techniques

TB laboratory capacity in the Region continues to improve and a number of positive developments have been observed. Coverage of first-line drug-sensitivity testing (DST) for new cases in the Region reached 97% in 2014 –the highest of all WHO regions. Uptake of rapid diagnostic techniques is increasing quickly: by the end of 2014, rapid molecular tests (line probe assays or Xpert MTB/RIF) were available in 41 countries in the Region. A regional algorithm on the introduction of new diagnostic techniques in confirming the diagnosis of TB, MDR-TB and XDR-TB is being finalized and will support laboratories and clinicians working in the field.

Guidance is also given on maintaining quality and safety standards in laboratories, including the interpretation of unclear results.

There is strong commercial interest in the field and several rapid diagnostic tools are in the pipeline. The recent GenoType MTBDRsl VER 2.0 can rapidly and reliably detect resistance to fluoroquinolones and second-line injectable drugs, including kanamycin; it is now being recommended as an alternative to phenotypic culture-based methods (for initial testing). The inclusion of pyrazinamide in the shorter MDR-TB regimen has been systematically reviewed, as resistance is significantly associated with rifampicin resistance. This is a problem, as available sensitivity testing for pyrazinamide is not endorsed by WHO due to false-negative or false-positive and unreliable results.

Several challenges remain, including a significant gap in coverage of second-line DST for confirmed MDR-TB cases across the Region. Human resource constraints remain a problem in some countries, and access to sophisticated equipment to diagnose M/XDR-TB cases is still limited in peripheral laboratories.

Discussion

- The cost of maintaining biosafety equipment, which is not covered by the GFATM, is compounded by a lack of qualified engineers. Special equipment needs to be calibrated, which is proving complicated logistically. New molecular tests have internal quality control, adding to the cost. DST for the second-line drugs (including line probe assays) is nevertheless critical in view of the introduction of short-treatment regimens and new drugs.
- Quality assurance of laboratories that perform DST may be problematic, but external quality assurance mechanisms are intended to resolve these issues. Clinical laboratory performance certificates are not compulsory for new line probe assay testing methods and no overall certificate of accreditation is currently available for new diagnostic methods. This could be diminishing the DST capacity of peripheral units compared to standard reference laboratories. Countries' standard reference laboratories should be involved in DST for second-line drugs, including new methods. Overall strengthening should consider not only laboratories' capacity, but also the general diagnostic network in countries.
- Reports of sensitivity testing for pyrazinamide on solid media should be interpreted with caution, as the low pH required makes this method technically challenging.
- Clinician education on new diagnostic methods (methodology, clinical role and interpretation) is insufficient. Clinicians in some countries doubt the reliability of new diagnostic techniques and often include more traditional testing methods in everyday patient management. Clinicians should be trained by standard reference laboratories and other organizations to help them understand and use new diagnostic tools.

Digital health interventions in support of MDR-TB prevention and care

WHO established the Global Task Force on Digital Health for TB to advocate for, and support the development of, digital health innovations in global efforts to improve TB care and prevention. New information and communication technologies present opportunities for innovative approaches to support TB efforts in patient care, surveillance, programme management and electronic learning.

A conceptual framework describes four functions that have particular relevance to management of drug-resistant TB:

- patient care: video-observed therapy and medication monitors can facilitate patient compliance;
- programmatic management: so-called connected diagnostics (such as eTB Manager) allow more efficient management of data from diverse diagnostic technologies and improved drugs-supply management;
- drug surveillance: adverse events can be monitored to facilitate active TB drug-safety monitoring and management; and
- eLearning: several tools can help to improve health care workers' capacity to make decisions on clinical care that are informed by improved access to data and knowledge.

Building the evidence base for these interventions when applied on a large scale will enable the development of stronger policies and increase uptake by country programmes of concepts and products with proven effectiveness.

New drugs and regimens: an update on policies, supply and forecasting

WHO PMDT policies and guidance, including so-called new drugs and shorter treatment regimens

In November 2015, WHO convened a guidelines development group to update its policy recommendations on the treatment of drug-resistant TB in accordance with the requirements of the WHO Guidelines Review Committee. The resultant 2016 recommendations include the following notable changes.

- A shorter MDR-TB treatment regimen is recommended for adults and children for programmatic use, under specific conditions.
- Medicines used in the design of longer MDR-TB treatment regimens are now grouped differently, based on current evidence on their effectiveness and safety. Clofazimine and linezolid are now recommended as core second-line medicines in the MDR-TB regimen, while p-aminosalicylic acid is an add-on agent (Group D1). Bdq and Dlm (Group D2) are recognized as add-on agents if the minimum of effective TB medicines (five effective drugs during the intensive phase from groups A, B and C) cannot be designed to reach the minimum of five drugs in the regimen.
- MDR-TB treatment is recommended for all patients with rifampicin-resistant TB, regardless of confirmation of isoniazid resistance.
- Specific recommendations are made on the treatment of children with rifampicin-resistant or MDR-TB.
- Clarithromycin and other macrolides are no longer included among the medicines to be used for the treatment of rifampicin-resistant and MDR-TB.
- Evidence-informed recommendations on the role of surgery are now included. There is no change in the role of new drugs – Bdq and Dlm – which have now been assigned to a specific subgroup of add-on agents.

Evidence on the treatment of isoniazid-resistant TB and delay in starting MDR-TB treatment could not address respective population, intervention, comparison and outcome questions. There

were very few published studies on the treatment of *M. bovis* and the regimens differed too much, precluding any attempt to formulate recommendations on clinical use. Current guidance did not indicate a need to update the policy on use of rapid diagnostics for rifampicin-resistant TB, monitoring of treatment response, duration of longer MDR-TB regimens, delay in starting antiretroviral therapy in MDR-TB patients with HIV infection or models of care. The 2011 recommendations will continue to apply to these aspects of PMDT until future research conducted to update WHO policy shows a need for revision.

The Global Drugs Facility (GDF): drug supply and forecasting

Prices of several second-line drugs continue to fall. The current average cost of a standard 20-month MDR-TB regimen has reduced by 43% since 2012. The USAID Bdq donation programme is available to all GFATM recipient countries and is distributed free of charge through the GDF on the condition that the countries meet WHO policy guidelines on Bdq use. Dlm can be purchased from the GDF at a special reduced price (US$ 1700 for a six-month course) by the same countries. Information on adverse effects for Dlm has to be submitted to the manufacturer via the GDF.

Special transition plans and technical support are provided to countries who will transition from GFATM support and six countries in the Region on the GDF's high-priority list (Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Ukraine and Uzbekistan). While the GDF meets a number of challenges, slow uptake of new and repurposed drugs is of major importance, as it has a direct effect on market price. In addition, regulatory barriers are more commonly encountered in the European Region than other regions.

Earlier GDF involvement when new regimes are approved by WHO would help reduce waste and facilitate the availability of proper drug formulations. Practical considerations such as the total quantity of drugs procured by countries and production times and shelf lives are important market factors: for example, Dlm has a longer shelf life (five years) than Bdq (two, although it is expected to be three by the end of 2016). Small orders are accommodated from a strategic rotating stockpile to reduce lead times and smooth out demand, offering some reassurance to manufacturers. Linezolid and Bdq have recently been added to the strategic rotating stockpile and Dlm will soon be added; p-aminosalicylic acid will probably be phased out by 2017.

Reliable forecasting and the use of dynamic early warning systems by countries is essential to avoid stock-outs. Recent trends in the Region, however, show a tendency towards significant overstocks and wastage. Supply planning requires good quality data, national compliance with standard treatment guidelines and accurate inventories. The recent introduction of new drugs and regimens has made planning even more complex.

The GDF strongly recommends that countries use QuanTB, an electronic forecasting, quantification and early warning tool that is designed to improve procurement processes, ordering and planning for TB treatment. Created by the USAID-funded Systems for Improved Access to Pharmaceutical and Services programme, QuanTB is a downloadable desktop tool that transforms complicated calculations into a user-friendly dashboard displaying key information for managing medicines. The software can easily be downloaded from the programme website.[2] Adopting an EWS will translate into significant cost savings, as manufacturers do not take back cancelled orders and the risk of having expired stock is averted.

[2] SIAPS. Systems for Improved Access to Pharmaceutical and Services programme [website]. Arlington (VA): SIAPS; 2016 (http://siapsprogram.org, accessed 22 September 2016).

Experiences from the Regional Office

The Regional Office has worked very closely with important partners such as USAID, the GDF and Médecins Sans Frontières to scale-up rapid diagnostic methods and access to new drugs, while setting a consistent regulatory and quality assurance framework. It has supported Member States in updating policy guidelines on shorter treatment regimens and clinical use of Dlm and Bdq, and has offered technical support on hospice end-of-life care. Ten Member States have introduced Bdq and Dlm and several others a range of other second-line drugs.

Many challenges that restrict access to new drugs are still evident in the Region, including: regulatory, legislative and importation barriers; the high cost of longer regimens, which include expensive second-line drugs; safety and toxicity concerns (especially in children), together with inadequate capacity for pharmacovigilance and active drugs safety and monitoring; lack of reliable DST for all second-line drugs; confusion in Russian-speaking countries due to slow translation of important product information; and the fast pace of guideline updates.

Discussion

- Mycobacterial drug-resistance patterns in the Region must be taken into account before the shorter nine-month regimen for MDR-TB is adopted by countries.
- Funding mechanisms are constantly evolving and shifting. USAID, for example, is continuing to support the rGLC/Europe: about 50% of total funding is from USAID, although specific country missions are funded through the GFATM. Sourcing of funds to address increasing migrant populations in Europe is becoming more pressing and urgent.
- The lack of a standardized approach to data collection is a key problem for medicine logistics and supply in countries. The adoption of an early warning system has met with some resistance in the Region. Quantification of supplies is expected to be strengthened in the next couple of years.
- Practical approaches to reduce wastage of second-line drugs include splitting orders for a year and not a full cohort, providing alternative drug packaging and reducing bottlenecks at customs clearance. Discordant treatment regimens often hamper accurate forecasting of medicines needs.
- Bdq is preferred to Dlm in the Region because: Dlm is not donated free of charge; MDR-TB coordinators have a personal preference for Bdq; Bdq has been longer on the market and has more active marketing support from the manufacturer; Bdq has easily availability as it has been registered in more countries; and the twice-daily dosage for Dlm increases patient supervision overheads.
- The mandate of rGLC/Europe in advising countries on new drugs and regimes was argued on the following grounds: scientific evidence on the effectiveness of these interventions is still evolving and being accumulated; there is no one body deciding if the pharmacovigilance conditions set by WHO are in place and the consequent funding implications; and national governments are the decision-makers and clinicians are ultimately responsible for the treatment of patients.

Childhood TB: new diagnostics and treatment

TB is difficult to diagnose in children and underdetection remains a major challenge. It is estimated that only one third of paediatric cases in the Region are detected. MDR-TB in children

is a new phenomenon and results from transmission from an adult source. The use of preventive therapy in such situations is as yet unclear. A regional working group is leading on key issues and will provide technical assistance on updating the management of TB in children.

Experience on the use of the new Xpert MTB/RIF as an initial diagnostic test for children is accumulating and is now recommended. Studies have shown that it is 40% more sensitive than smear microscopy in this age group, but it is clear a negative test should not exclude a diagnosis of TB.

Child-friendly dispersible fixed-dose drug combinations (rifampicin 75 mg + isoniazid 50 mg + pyrazinamide 150 mg, and rifampicin 75 mg + isoniazid 50 mg) and paediatric doses for ethambutol are now available and comprise welcome additions to the GDF catalogue.

The guidelines development group has only recently reviewed the use of Dlm in children older than 6 years, and conclusions are not yet available. Reports published to date on as-yet limited experience through the compassionate use programme (age cohort 8–17 years) have indicated good tolerance and mild adverse events. No information on the use of Bdq in children has been reported officially.

Discussion

- Evidence to promote the use of new drugs in the preventive treatment of child contacts of MDR-TB cases is insufficient, and the results of studies will take time to be released. This raises ethical issues on how to deal with this situation.
- In light of the recent scarcity of tuberculin supplies, some countries seem to be shifting towards the interferon gamma release assay. There is insufficient data to suggest that this is either preferable or superior to tuberculin testing.

Country-specific research

The End TB Strategy highlights the critical role research and innovation efforts must play to break the current trajectory of the TB epidemic. The synergistic use of new diagnostic techniques, new anti-TB drugs and shorter drug regimens will have a lasting effect only if used to support strong TB programmes. Country-specific research needs to be led by a national TB research agenda; a technical assistance toolkit has been developed for this purpose and will soon be piloted in two countries in Africa and Asia.

Discussion

- A European TB research initiative is planned to be in place for November 2016, with the call for membership of the core group being launched in October 2016. The initiative will link to rGLC/Europe and the European TB laboratory initiative. It is suggested that country representatives be encouraged to apply.
- Language barriers are evident in some countries.

The role of civil society in implementing the End TB Strategy

The importance of civil society groups should not be underestimated, as their activities complement all three pillars of the End TB strategy. The TB Europe Coalition is very active and has recently launched TB People, a new eastern European and central Asian network of people with experience of TB. The Coalition is also participating in the project on strengthening health

systems for effective TB and drug-resistant TB control in that region and is responsible for grassroots advocacy of the civil society organization Alliance for Public Health in Ukraine, which serves as a project implementer on behalf of the Coalition.

Civil society groups can mobilize their networks to reach marginal groups, especially when resources are limited. They are also very adept at demanding action by governments and can use local experiences to direct operational research to define and address gaps in the system.

Discussion

- The WHO Framework of Engagement with Non-state Actors has been launched with a view to strengthening engagement. To date, the TB Alliance is still not on the WHO register of non-state actors.[3]
- A large number of non-state actors have contributed to the high quality of treatment and care in the Region. Civil society groups may have a bigger impact if they are allowed to adopt the role of active partner in TB care, rather than taking a purely activist position.
- New communication approaches that exploit social media can provide new solutions through innovation. These may be helpful to civil society groups, especially those that encounter difficulties in some countries.
- Stigma and fear of infection remain important issues that determine the reluctance of volunteers to work in this field.

[3] According to a comment from the rGLC/Europe Secretariat based on information from the TB Alliance, the Alliance for Public Health has now started registration.

Recommendations and action points for the rGLC/Europe: the next steps

By the end of the meeting, rGLC/Europe members had agreed on recommendations (reflecting the pillars and format of activities under the End TB Strategy) and further action points to be followed up.

Recommendations for WHO and partners

1. Integrated, patient-centred care and prevention

A. Diagnosis of TB, including universal DST testing

1. Countries must be encouraged to expedite coverage of PMDT services, with necessary capacity-strengthening of laboratory and diagnostic networks.
2. Countries must undertake demand-forecasting for laboratory services (keeping universal access to PMDT services in focus) and revise national laboratory and PMDT scale-up plans aligned with the national strategic plan that aim to achieve universal DST.
3. Supranational reference laboratories should offer external quality assurance proficiency testing for all diagnostic methods and drugs used in the country.

B. Treatment of all people with TB

1. A shorter MDR-TB treatment regimen is recommended in the Region, under specific conditions:
    a. high-quality implementation of DST for second-line drugs (second version genotyping test and parallel MGIT test for second line drugsL, which excludes pre-XDR-TB and XDR-TB patients) is in place;
    b. clofazimin is registered and available on the market in the country; and
    c. start dates for phase-in/out of regimens/medicines are realistic, with the respective phase in/out plans available in countries.
2. Prevention of drug-resistant TB should be boosted by improving the quality of conventional TB treatment.
3. Special courses on new drugs and treatment regimens should be organized for NTP managers, M/XDR-TB coordinators, consultants and partners. These should include workshops to train people on the introduction and scaling-up of new medicines, regimens and drug management (involving WHO, rGLC/Europe and GDF) and webinars to share experience from countries on new medicines, treatment regimens and paediatric TB.
4. Countries should be encouraged and supported to further boost integration of TB prevention and care in primary health care, shifting to ambulatory models of care and making health systems stronger and more resilient.
5. Support to physicians on medical management of patients on Group C and D2 drugs should be strengthened through online consultations (possibly in collaboration with the European Respiratory Society); bilingual support (English and Russian languages) should be considered.
6. A specific country-tailored approach should be followed with strengthened follow up of rGLC/Europe missions, with the emphasis on implementation of actionable recommendations.

2. Bold policies and supportive systems

A. Political commitment with adequate resources for TB care and prevention

1. National strategic TB plans should be adapted in line with the global End TB Strategy and the TB action plan for the Region 2016–2020.
2. Emphasis should be placed on coordination, with greater and more systematic engagement with partners on the ground to effectively address bottlenecks, scale-up short-treatment regimen and new-medicines implementation, and strengthen PMDT.
3. The rGLC/Europe missions should be planned well in advance in close discussion with the NTP. The content, tailored terms of reference and timing of each mission should be based on programme priorities (such as ongoing grant-making and urgent recommendations from the previous rGLC/Europe mission).
4. Where possible, NTP managers' meetings should be combined with those of the rGLC/Europe, with NTP representatives invited to face-to-face meetings.
5. A feasible and systematic mechanism for following up on rGLC recommendations should be established at country level – follow up only during country missions by the fund portfolio manager is insufficient.
6. The pool of consultants should continue to increase, ensuring consistency of consultants' work during subsequent missions to the country and, where necessary, including a laboratory specialist in the mission.

B. Engagement of communities, civil society and public and private care providers

1. Partnerships should be promoted and the complementary advantages of different players at country and regional levels identified.
2. The possibility of GFATM allocating funds under the NTP for migrants with MDR-TB should be investigated.
3. Sharing of good practices between countries, including information on new drugs, new models of care and other experiences, should be continued.
4. Links should be made with country-based partners in Technical Assistance provision.
5. Meaningful engagement of the regional network(s) (TB Europe Coalition, TB People and others, as well as national civil societies) should be ensured throughout the whole process, from design and planning, to implementation of mission recommendations, through to monitoring and evaluation.
6. Transparency of information can be achieved by making mission reports accessible to all stakeholders, including regional and local civil society, with the proviso that steps are taken to avoid the disclosure of confidential information.
7. The WHO Framework of Engagement with Non-state Actors should be used as the tool through which civil society organizations can be registered on the database of non-state actors and achieve better coordination.

C. Universal health coverage policy, framework for case notifications, vital registration, quality and rational use of drugs

1. The introduction of new and repurposed drugs should be scaled-up at country level.
2. The conversation on laboratory and diagnostic network enhancement should be expanded in countries.
3. Enhanced technical assistance from the Regional Office and rGLC/Europe is required to implement effectively Group C and D2 drugs according to the latest WHO guidelines on PMDT in all Member States, with a special focus on MDR-TB high-burden countries. Technical assistance should include methodological support on updates to national plans, guidelines, drug forecasting, training and patient management.
4. Training on the introduction and use of new TB drugs is required for prospective consultants from high-burden countries, who will serve as country focal points and

increase countries' capacity in relation to TB drugs management and clinical management of TB patients.

5. The rGLC/Europe, GDF, GFATM and WHO should promote the use of quality-assured drugs in Member States.
6. The use of Dlm should be promoted.
7. A working group on standardization of data requirements, collection, validation and analysis for data-driven forecasting, quantification, supply planning, procurement and early warning should be established, and a medicines utilization review carried out.
8. The establishment of a functional early warning system in the Region should be promoted, to include quarterly reporting to rGLC/Europe, the Regional Office, GDF and other stakeholders.
9. The procurement of quality-assured TB medicines in countries graduating from GFATM support should be promoted through rGLC/Europe consultancies, workshops, meetings, and engagement of civil society and advocacy groups. Technical assistance is available to manufacturers in the Region willing to obtain WHO prequalification for their products (Technical assistance from the USAID-funded PQM project).
10. A data-driven, needs-based approach to procurement (not cohort-based) should be promoted. This will require review of patient-related data that are essential for medicine forecasts and orders – the number of cases enrolled and projected per regimen during a particular period of time – by rGLC/Europe consultants in conjunction with the GDF. Validation of countries' projections against actual capacity to diagnose and enrol patients will constitute the drug management component of the rGLC/Europe mission reports.
11. Countries require phase in/out plans for new medicines and regimens.
12. Annual regional workshops on forecasting, quantification, supply planning and early warning that combine training with experience-sharing should be held for trainers, consultants and NTP drug coordinators. The GDF will provide technical leadership and facilitation.

3. Intensified research and innovations

1. Research and innovation, including new drugs and studies on the duration of treatment, should be encouraged.
2. Digital health should be included in the PMDT programme.
3. WHO should be the gatekeeper for implementation of innovations in the Region, providing oversight and supporting partners to ensure coordination across the Region is regular and systematic.

Action points for rGLC/Europe

Action points for rGLC/Europe are shown in Table 1.

Table 1. Action points for rGLC/Europe

	Action points	Timeline
1.	The rGLC/Europe will contribute to the agenda and implementation of the European TB research initiative	By November 2016
2.	The drugs management component will be included once again in rGLC/Europe reports, with a focus on patient-related data, while GDF will do forecasting of medicines	By September 2016
3.	Consultants of rGLC/Europe will emphasize to countries the importance of not	From September

	Action points	Timeline
	procuring medicines for the entire cohort of the patients	2016
4.	Surveillance/surveys data will be used for rGLC/Europe reports and analysis	From September 2016
5.	Askar Yedilbayev, Gunta Dravniece, Maya Kavtaradze, Denis Falzon and Andrei Dadu will work on drugs forecasting and estimation of drug needs	By December 2016
6.	The rGLC/Europe will look through countries' procurement order requests (within three working days)	From August 2016
7.	Special courses will be organized for NTP managers, M/XDR-TB coordinators, consultants and partners on new drugs and treatment regimens: a. an internal webinar to train people on new drugs, new regimens and drugs management (WHO/rGLC Europe/GDF); and b. webinars to share experience from countries (on new drugs, treatment regimens and paediatric TB)	From November 2016
8.	A thorough mechanism to follow up on the implementation of recommendations and develop actions on how to address chronic gaps will be developed – this may include conference calls with countries or the supranational reference laboratory, and ad hoc technical assitance missions	By January 2017
9.	The rGLC/Europe will plan country-specific call with standard operating procedures on drugs management for countries to introduce and set the early warning system (by GDF)	From September 2016
10.	Specific recommendations will be made on the shorter treatment of children with MDR-TB and using new drugs in this special situation	From September 2016
11.	The rGLC/Europe will discuss confidentiality of reports and civil society organization-friendly procedures for obtaining report summaries	By December 2016
12.	Strong collaboration with the Regional Collaborating Committee and civil society organizations will continue through engagement at meetings, quantification of needs, and identification of the need for technical assistance and monitoring visits to countries. The WHO Framework of Engagement with Non-state Actors will be offered to civil society organizations to support them through, for instance, the registration process.	From September 2016
13.	Key messages for high-level advocacy will be provided, with strong involvement of the European TB research initiative	From November 2016 (once the European TB research initiative is established)
14.	TB-relevant health system challenges will be addressed jointly with the TB regional eastern Europe and central Asia project	From August 2016
15.	The approach of consultants operating at country level will be harmonized	From September 2016
16.	Recommendations will be rationalized and limited to actionable items through an analysis of causes and development of proposals for practical solutions	From September 2016
17.	The rGLC/Europe should play a bigger role in distributing the latest recommendations, evidence, etc. It may do this through, for example, webinars on guidelines and best practices from countries	From September 2016
18.	The possibility of extending the duration of rGLC/Europe missions from five	From September

	Action points	Timeline
	working days to a longer period, at least for priority countries such as Tajikistan, Ukraine and Uzbekistan, will be explored	2016

Supporting documents

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WHO Regional Office for Europe (2015). Tuberculosis action plan for the WHO European Region 2016–2020. Copenhagen: WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0007/283804/65wd17e_Rev1_TBActionPlan_150588_withCover.pdf?ua=1, accessed 25 September 2016).

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World Health Organization (2015). Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. Geneva: World Health Organization (apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf, accessed 25 September 2016).

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World Health Organization (2016). The use of molecular line probe assay for the detection of resistance to second-line anti-tuberculosis drugs. Policy guidance. Geneva: World Health Organization (http://www.who.int/tb/areas-of-work/laboratory/policy_statements/en/, accessed 25 September 2016).

World Health Organization (2016). WHO treatment guidelines for drug-resistant tuberculosis 2016 update. Geneva: World Health Organization (http://www.who.int/tb/MDRTBguidelines2016.pdf, accessed 25 September 2016).

Annex 1

PROGRAMME

	4 August 2016	
09:00–09:30	**Session 1**	
	1. Opening and welcome	Dr Masoud Dara
	2. Objectives, agenda, modus operandi and declaration of interests	Dr Andrei Mariandyshev (chair of rGLC/Europe)
	3. Election of chair for event	
09:30–10:45	**Session 2**	
	4. PMDT contributions to Sustainable Development Goals agenda	Dr Martin van den Boom Dr Ogtay Gozalov
	5. Follow-up on previous rGLC/Europe recommendations	Dr Sevim Ahmedov
	6. The rGLC/Europe role in supporting implementation of End TB Strategy via technical assistance on Global Fund-supported projects	
	7. United States Government national action plan to combat MDR-TB	
	Discussion	
11:00–13:00	**Session 3. New treatment regimens**	
	8. Update on new drugs	Dr Martin van den Boom
	9. GDF role in supply of new drugs	Dr Andre Zagorski
	10. Update on WHO PMDT policies and guidance, including so-called new drugs and shorter treatment regimens and support of rGLC/Europe on scaling-up new and shorter regimens in the Region	Dr Dennis Falzon Dr Maya Kavtaradze
	11. Digital health interventions in support of MDR-TB prevention and care	
	12. Anti-TB medicines forecasting, quantification and early warning system in light of introduction and implementation of new medicines and treatment regimens: challenges and possible solutions	
	Discussion	
14:00–14:45	**Session 4**	
	13. Updates from European TB laboratory initiative	Dr Soudeh Ehsani
	14. So-called new diagnostic techniques: policy recommendations	Mr Riccardo Alagna
	Discussion	
14:45–15:30	**Session 5**	
	15. Childhood TB: new perspectives on diagnostics and treatment, including experience of Bdq/Dlm usage for children (experience in Belarus and Latvia)	Dr Malgosia Grzemska Dr Martin van den Boom Ms Medea Gegia
	Discussion	
	Session 6	
15:30–16:00	16. Civil society involvement in implementation of End TB Strategy	
	Discussion	Ms Yuliya Chorna

16:30–17:00	**Session 7**	
	17. Promoting and implementing country-specific research Discussion	Dr Christian Lienhardt (via Skype/WebEx)
17:00–17:30	**End of Day 1/wrap-up session**	
	5 August 2016	
09:30–11:00	**Session 8**	
	18. National TB control programme reviews for 2016/2017	Dr Ogtay Gozalov
	19. rGLC/Europe missions update: tentative dates, consultants, countries	Dr Malgosia Grzemska Ms Medea Gegia
	20. rGLC/Europe: way forward, priorities, future arrangements, long-term support (including financial) for drug-resistant TB implementation in the Region and next topics	
	Discussion	
11:15–12:15	**Session 9**	
	21. Development of rGLC/Europe recommendations	Dr Ogtay Gozalov
	22. Approval of current rGLC/Europe mission reports	
12:15–12:30	**Session 10. Closure and next steps**	Dr Andrei Mariandyshev Dr Masoud Dara

Annex 2

PARTICIPANTS

A. The rGLC/Europe members and supporters	E. The Global Fund Against AIDS, Tuberculosis and Malaria
1. Dr Andrei Mariandyshev (chair) 2. Dr Manfred Danilovits 3. Dr Gunta Dravniece 4. Dr Askar Yedilbayev 5. Dr Sabine Rüsch-Gerdes 6. Dr Andrei Mosneaga (excused) 7. Dr Vaira Leimane (excused) 8. Dr Aamir Khan (excused, via WebEx), 9. Dr Kai Blondal (excused) 10. Dr Soeren Thybo (excused) 11. Dr Elmira Gurbanova	1. Dr Mohammed Yassin (via Skype/WebEx) 2. Dr Artashes Mirzoyan
B. WHO Regional Collaborating Committee representative	**F. United States Agency for International Development**
1. Ms Yulia Chorna	1. Dr Sevim Akhmedov
C. European TB laboratory initiative representative: core group secretariat and external laboratory consultant	**G. WHO Regional Office for Europe**
1. Dr Soudeh Ehsani (via WebEx) 2. Mr Riccardo Alagna	1. Dr Martin van den Boom 2. Dr Andrei Dadu 3. Dr Masoud Dara 4. Dr Soudeh Ehsani 5. Dr Nedret Emiroglu 6. Dr Ogtay Gozalov 7. Ms Anne-Brigitte Gradman 8. Ms Elizabeth Neville 9. Mr Stefan Litvinjenko (reporter) 10. Dr Ann Galea (reporter)
D. Global Drugs Facility	**H. WHO headquarters**
1. Mr Andre Zagorski 2. Dr Maya Kavtaradze	1. Dr Dennis Falzon 2. Dr Malgosia Grzemska 3. Dr Medea Gegia 4. Dr Christian Lienhardt (via WebEx)

Annex 3

PRE-RGLC/EUROPE MISSION FORM

1.1. Incidence, prevalence and mortality rates of TB (past three years): civilian sector

Year	Incidence	Prevalence	Mortality
2013			
2014			
2015			

1.2. Incidence, prevalence and mortality rates of TB (past three years): prison sector

Year	Incidence	Prevalence	Mortality
2013			
2014			
2015			

2.1. TB case notification (past three years): civilian sector

	2013		2014		2015	
Case notifications	**Total**	**%**	**Total**	**%**	**Total**	**%**
New cases						
Smear-positive						
Smear-negative						
Smear unknown						
Extrapulmonary TB						
Other						
Total new						
Retreatment cases						
Relapse						
Treatment after failure						
Treatment after default						
Other						
Total retreatment						

2.2. TB case notification (past three years): prison sector

	2013		2014		2015	
Case notifications	**Total**	**%**	**Total**	**%**	**Total**	**%**
New cases						
Smear-positive						
Smear-negative						
Smear unknown						
Extrapulmonary TB						
Other						
Total new						
Retreatment cases						
Relapse						
Treatment after failure						

Treatment after default
Other
Total retreatment

3.1. Treatment outcomes for MDR-TB cohort (recent two years): civilian sector

For years:

Registration group	Cured	Treatment completed	Died	Failed	Lost to follow up	Not evaluated	Total
New							
Relapse							
After default							
After failure of Category I treatment							
After failure of Category II treatment							
Other retreatment, or unknown retreatment[a]							
Total							

[a] Unknown retreatment is a previously treated case but without information on the outcome of previous treatment.

3.2. Treatment outcomes for MDR-TB cohort (recent two years): prison sector

Registration group	Cured	Treatment completed	Died	Failed	Lost to follow up	Not evaluated	Total
New							
Relapse							
After default							
After failure of Category I treatment							
After failure of Category II treatment							
Other retreatment, or unknown retreatment[a]							
Total							

[a] Unknown retreatment is a previously treated case but without information on the outcome of previous treatment.

4.1. Notified cases of MDR-TB, YYYY-YYYY: civilian sector

Year	TB-S	Poly	RR/MDR-TB	XDR-TB	%
2013					
2014					
2015					

4.2. Notified cases of MDR-TB, YYYY-YYYY: prison sector

Year	TB-S	Poly	RR/MDR-TB	XDR-TB	%
2013					
2014					
2015					

5.1. Number of patients started on treatment with second-line drugs, under GFATM projects

Cohort/year	No patients notified	Number enrolled	Still on treatment	Success	Lost to follow up	Failure	Died	Not evaluated
TOTAL								
New cohorts (planned for YYYY)								

5.2. Number of patients started on treatment with second-line drugs, non-GFATM projects

Cohort/year	No patients notified	Number enrolled	Still on treatment	Success	Lost to follow up	Failure	Died	Not evaluated
TOTAL								
New cohorts (planned for YYYY)								

6.1. Treatment outcomes of DS-TB, YYYY and YYYY: civilian sector

Year		Number of patients notified	Treatment completed	Cured	Death	Lost to follow up	Failure	No TB	Not evaluated	Total
New	SS+									
	SS-									
	EP									
	Total									
Retreatment	Relapse SS+									
	Relapse SS-									

Year		Number of patients notified	Treatment completed	Cured	Death	Lost to follow up	Failure	No TB	Not evaluated	Total
	Default SS+									
	Default SS-									
	Failure									
	Other									
	EP									

Year		No patients notified	Treatment completed	Cured	Death	Lost to follow up	Failure	No TB	Not evaluated	Total
New	SS+									
	SS-									
	EP									
	Total									
Retreatment	Relapse SS+									
	Relapse SS-									
	Default SS+									
	Default SS-									
	Failure									
	Other									
	EP									

6.2. Treatment outcomes of DS-TB, YYYY and YYYY: prison sector

Year		Number of patients notified	Treatment completed	Cured	Death	Lost to follow up	Failure	No TB	Not evaluated	Total
New	SS+									
	SS-									
	EP									
	Total									
Retreatment	Relapse SS+									
	Relapse SS-									
	Default SS+									
	Default SS-									
	Failure									

Year		Number of patients notified	Treatment completed	Cured	Death	Lost to follow up	Failure	No TB	Not evaluated	Total
	Other									
	EP									

Year		No patients notified	Treatment completed	Cured	Death	Lost to follow up	Failure	No TB	Not evaluated	Total
New	SS+									
	SS-									
	EP									
	Total									
Retreatment	Relapse SS+									
	Relapse SS-									
	Default SS+									
	Default SS-									
	Failure									
	Other									
	EP									

7. Please provide most recent data on DST performed and accumulated at national refernce laboratory.

8. Please provide data on RR, MDR-TB and XDR-TB registered in YYYY and YYYY, if available, by patient type and % of them started on appropriate treatment.

8.1 By treatment regimen

MM/YYYY	MDR-TB Regimen 1	MDR-TB Regimen 2	MDR-TB Regimen 3	MDR-TB Regimen 4	MDR-TB Regimen 5	MDR-TB Regimen 6	MDR-TB Regimen 7

If information regarding number or percentage of cases per treatment regimen is not available, please provide information below about percentage use of medicines.

8.2.1. Number of cases started treatment

MM/YYYY	Number of cases started treatment

8.2.2. Percentage use

Medicine	Percentage use

9. Please provide data on the number of MDR-TB and XDR-TB patients enrolled into therapy with second-line drugs (rGLC and non-rGLC cohort). Please provide a separate column on patients accessing bedaquiline- and delamanid-containing regimens.

10.1. Availability and stock-out of second-line drugs (GDF), national summary data as of MM/DD/YYYY

Name	Type	Expiration	NTP office	HARC	MSF-F	Other (indicate)
Kanamycin 1000	Vial					
Amikacin 500–2.0 ml	Vial					
Capreomycin 1000	Vial					
Levofloxacin 250 mg	Tablet					
Levofloxacin 500 mg	Tablet					
Levofloxacin 750 mg	Tablet					
Moxifloxacin 400 mg	Tablet					
PASER 4 g	Sachet					
Cycloserine 250 mg	Tablet					

Name	Type	Expiration	NTP office	HARC	MSF-F	Other (indicate)
Prothionamide 250 mg	Tablet					
Amoxicillin clavulanic acid 500/125 mg	Tablet					
Amoxicillin clavulanic acid 875/125 mg	Tablet					
Pyrazinamide 400 mg	Tablet					
Pyrazinamide 500 mg	Tablet					
Bedaquiline 100 mg	Tablet					
Clofazimine 100 mg	Tablet					
Linezolid 100 mg	Tablet					
Imipenium/cilastatin 500 mg	Vial					
Meropenem 1000 mg						

10.2. Availability and stock-out of second-line drugs (other source), national summary data as of MM/DD/YYYY

Name	Type	Expiration	NTP office	HARC	MSF-F	Other (indicate)
Kanamycin 1000	Vial					
Amikacin 500–2.0 ml	Vial					
Capreomycin 1000	Vial					
Levofloxacin 250 mg	Tablet					
Levofloxacin 500 mg	Tablet					
Levofloxacin 750 mg	Tablet					
Moxifloxacin 400 mg	Tablet					
PASER 4 g	Sachet					
Cycloserine 250 mg	Tablet					
Prothionamide 250 mg	Tablet					
Amoxicillin clavulanic acid 500/125 mg	Tablet					
Amoxicillin clavulanic acid 875/125 mg	Tablet					
Pyrazinamide 400 mg	Tablet					
Pyrazinamide 500 mg	Tablet					
Bedaquiline 100 mg	Tablet					

Name	Type	Expiration	NTP office	HARC	MSF-F	Other (indicate)
Clofazimine 100 mg	Tablet					
Linezolid 100 mg	Tablet					
Imipenium/cilastatin 500 mg	Vial					
Meropenem 1000 mg						