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Joint WHO headquarters/ WHO Regional Office for Europe experience-sharing workshop on the introduction of new drugs for the treatment of multidrug-resistant tuberculosis

Copenhagen, Denmark, 22–23 September 2015

ABSTRACT

In the interest of continuing and expanding the extensive work carried out so far in the WHO European Region under the *Consolidated action plan to prevent and combat multidrug- and extensively drug-resistant tuberculosis in the WHO European Region 2011–2015*, and within the framework of the commitments expressed in the new regional TB action plan for 2016–2020, a joint WHO headquarters/WHO Regional Office for Europe experience-sharing workshop was held in Copenhagen to bring together key actors contributing to the fight against drug-resistant tuberculosis. This report summarizes presentations and discussions from the workshop.

Keywords

EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS – prevention and control
TUBERCULOSIS, MULTIDRUG-RESISTANT – prevention and control
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Acronyms and abbreviations

ADR	adverse drug reaction
aDSM	active drug safety monitoring and management
AE	adverse event
AR	adverse reaction
Amx	amoxicillin
Bdq	bedaquiline
CC	(WHO) collaborating centre
CDC	(United States) Centers for Disease Control and Prevention
Cfz	clofazimine
Clr	clarithromycin
Cln	cilastatin
Clv	clavulanate
Cs	cycloserine
CUP	Compassionate Use Programme
Dlm	delamanid
DOT	directly observed treatment
DR–TB	drug-resistant tuberculosis
DSM	drug-safety monitoring
DST	drug-sensitivity testing
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiograph (testing)
EML	essential medicines list
ERS	European Respiratory Society
FLD	first-line drug
GDF	Global Drug Facility
GDI	Global Drug-resistant TB Initiative
GF	Global Fund (to Fight AIDS, Tuberculosis and Malaria)
GRADE	Grades of Recommendation Assessment, Development and Evaluation
GTB	(WHO) Global TB Programme
Ipm	imipenem
IRD	Interactive Research & Development
ISTC	International Standards for Tuberculosis Care
LDR	Laboratories, Diagnostics and Drug-resistance (Unit)
LPA	line probe assay
LZD	linezolid
M&E	monitoring and evaluation
Mfx	moxifloxacin
MoU	memorandum of understanding
MSF	Médecins Sans Frontières
MSH	Management Sciences for Health
MDR/XDR–TB	multidrug- and extensively drug-resistant tuberculosis
NRC	national reference centre
NRL	national reference laboratory
NTC	National Tuberculosis Centre
NTP	national TB (control) programme
PAS	para-aminosalicylate sodium
PCR	polymerase chain reaction (testing)
PIH	Partners in Health
PMDT	programmatic management of drug-resistant TB

PSI	Policy, Strategy and Innovations (Unit)
PV	pharmacovigilance
R	rifampicin
RCT	randomized controlled trial
rGLC	regional Green Light Committee
RR–TB	rifampicin-resistant TB
SAE	serious adverse event
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SLD	second-line drug
SNRL	Supranational Reference Laboratory
SRS	strategic rotating stockpile
STAG–TB	(WHO) Strategic and Technical Advisory Group for TB
TB	tuberculosis
ToR	terms of reference
UNDP	United Nations Development Programme
UNOPS	United Nations Office for Project Services
USAID	United States Agency for International Development
WRD	WHO-approved rapid diagnostics

Executive summary

In the interest of continuing and expanding the extensive work carried out so far in the WHO European Region under the *Consolidated action plan to prevent and combat multidrug- and extensively drug-resistant tuberculosis in the WHO European Region 2011–2015*,[1] and within the framework of the commitments expressed in the new regional TB action plan for 2016–2020, a joint WHO headquarters/WHO Regional Office for Europe experience-sharing workshop was held in Copenhagen to bring together key actors contributing to the fight against drug-resistant tuberculosis (DR–TB).

New drugs previously first-line repurposed drugs are being approved by regulatory authorities for use in treatment regimens for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB patients. WHO's Global TB Programme (GTB) issued interim policy guidance on the use of two new drugs (on bedaquiline (Bdq) in mid-2013 and delamanid (Dlm) in October 2014). However, limited data are available on the safety (both patient and drug) of these new medicines, and also on the safety and efficacy of the repurposed drugs listed under Group V in the WHO Companion Handbook to the 2011 *Guidelines for programmatic management of drug-resistant tuberculosis*.[2] Adequate provisions must be put in place for safe, rational and effective use of these drugs, in particular through the selection of eligible patients, design of effective regimens, and appropriate monitoring and evaluation (M&E) activities. Further issues for consideration include drug ordering, transportation and storage, as well as pharmacovigilance (PV), including active drug safety monitoring and management (aDSM) to rapidly detect potential drug adverse events (AEs).

The workshop forms part of a series planned by WHO headquarters for all six regions and related regional Green Light Committees (rGLCs), rGLC members and their respective rGLC secretariat focal points. They each play an essential role as primary contacts to guide and advise countries on the programmatic management of DR–TB (PMDT) to remain up to date on current WHO policy recommendations, in this case on the use of the new and repurposed anti-TB drugs, as well as encouraging countries and partners to make use of the rGLC mechanism to ensure compliance with WHO guidelines.

[1] Available at the WHO/Europe website: http://www.euro.who.int/en/about-us/governance/regional-committee-for-europe/past-sessions/sixty-first-session/documentation/working-documents/wd15-consolidated-action-plan-to-prevent-and-combat-multidrug-and-extensively-drug-resistant-tuberculosis-in-the-who-european-region-20112015.

[2] Available at the WHO website: http://www.who.int/tb/publications/pmdt_companionhandbook/en/.

Background

MDR/XDR–TB is a significant public health challenge in the WHO European Region, which has the lowest TB treatment success rates of all WHO regions. Key causes of MDR/XDR–TB are inappropriate treatment, inappropriate or incorrect use of anti-TB drugs, use of poor-quality medicines and transmission of drug-resistant infection, all of which contribute to drug resistance. Disease caused by resistant bacteria fails to respond to conventional, first-line drugs (FLDs), but can be treated and cured using second-line drugs (SLDs). However, such treatment options are limited, as is the availability of SLDs, which are more costly and can produce severe adverse drug reactions (ADRs) in patients.

Controlling DR–TB involves a combination of factors and requires a multifaceted approach, which can be achieved by:

- preventing MDR–TB as a first priority, involving continued targeted and effective TB care with FLDs in the first instance;
- ensuring timely access to diagnosis through rapid expansion in testing and detection of DR–TB cases, requiring consideration and coordination at health system level and beyond;
- ensuring there are no mistakes in clinical care or drug management (supply and administration), such as:
    - helping patients to adhere strictly to treatment regimens;
    - using high-quality drugs, correct formulations and prompt and adequate transportation, supply and storage of the drugs; and
    - implementing proper infection control procedures and response within facilities in which patients are treated and in high-risk areas (such as prisons and hospitals);
- sharing knowledge and good practices on all aspects of TB control, thereby aiming to improve PMDT through:
    - high-level commitment in terms of financing, combining domestic and international resources to ensure full coverage of DR–TB patients within national health financing mechanisms;
    - working in partnership with relevant actors in the health field and beyond to respond appropriately to DR–TB; and
    - taking into account (WHO) guidance on the management of DR–TB patients and diagnostic policies to inform scaled-up efforts to introduce new drugs to treat DR–TB safely and effectively.

Against this backdrop, the aims of the joint WHO headquarters/WHO Regional Office for Europe experience-sharing workshop on the introduction of new drugs for DR–TB treatment in the European Region were to:

a. exchange experiences relating to the introduction of new and/or repurposed DR–TB drugs, particularly in terms of challenges faced at operational level in various locations and settings;
b. update country representatives and partner organizations working in the DR–TB field as regards WHO policy guidance on introducing the new and repurposed DR–TB drugs into treatment regimens; and
c. discuss next steps in terms of these anti-TB drugs, focusing specifically on their introduction into programmatic use.

The final programme can be found at Annex 1, the scope and purpose at Annex 2, and participants at Annex 3.

Day 1. Tuesday 22 September 2015

Welcome and meeting objectives

Dr Martin van den Boom, Technical Officer for the WHO Joint Tuberculosis, HIV/AIDS and Hepatitis Programme, and Dr Fraser Wares (Laboratories, Diagnostics and Drug-resistance (LDR) Unit of the Global TB Programme (GTB)), welcomed participants to the workshop on behalf of acting Programme Manager Dr Masoud Dara, reminding participants that there was much to discuss in light of the regional DR–TB action plan for 2011–2015 and the new regional TB action plan for 2016–2020, with prevention and control of MDR/XDR–TB paramount on the agenda. Greetings were also passed on from the Director and all who had contributed to the background work for, and organization of, the two-day workshop were thanked, including colleagues and international partners.

Dr Wares declared the workshop an historic event and alluded to an element of "uncharted territory" associated with it; the workshop was tailored specifically to discussion of DR–TB, with the aim to use a "learning-by-doing" approach, sharing experiences of challenges faced at country level when introducing these new drugs, which are the first available in 40 years of TB treatment. However, the new and repurposed Group V drugs were being used in DR–TB treatment regimens despite only having undergone Phase 2 testing, making it all the more important that the rGLC members and partners attending the workshop(s) fulfil their role(s) to support countries in introducing into programmatic use these relatively unknown drugs safely, rationally and effectively, specifically taking into account PV issues. It was expressed that the next steps and the outcomes of the workshop discussions could also be used to benefit other WHO regions.

Dr Andrei Mariandyshev, Chair of rGLC Europe, was elected Chair for the workshop.

Session 1. Objective: to provide updates on current WHO global and regional policies, guidance and plans

Dr Martin van den Boom, Technical Officer for the WHO Joint Tuberculosis, HIV/AIDS and Hepatitis Programme

Update on new regional TB Action Plan 2016–2020

On behalf of Dr Masoud Dara, Dr van den Boom presented a short overview of the global and European TB burden(s), highlighting the positive (albeit slow) trend towards TB decline in the European Region. However, in 2013 the Region had the highest proportion of MDR–TB among both new and previously treated TB cases, with the 18 high-priority countries having the highest incidence. He also pointed out that the so-called "stabilization" of MDR–TB could not realistically be considered a positive trend, with such high levels. He provided detailed information regarding the spread of both disease and drug resistance, emphasizing that the focus on fighting TB needed to be across the board in order to make sustainable progress in TB prevention and care. He also presented an overview of the positive steps and achievements in combating MDR–TB (reduced prevalence, increased detection and treatment coverage, as well as broadening programme coverage from baseline small-scale pilot projects), and summarized

the key tenets for the GTB, outlining the core pillars and principles of the new TB action plan for the WHO European Region 2016–2020 and what they mean in terms of action areas and desired results.

Dr van den Boom reminded the workshop attendees of the encouraging nature of these overarching achievements and objectives, should anyone feel disheartened about the global picture of the fight against DR–TB; while much work remained to be done, significant progress had been achieved with the implementation of the current regional TB plan thus far. He thanked all involved – including the rGLC members – for their part in that progress, and acknowledged his fellow WHO Joint Tuberculosis, HIV/AIDS and Hepatitis Programme technical officer Dr Andrei Dadu and colleague Dr Colleen Acosta for their parts in preparing the introductory presentation, extending his gratitude on behalf of himself and Dr Masoud Dara to all partners and Member States.

Discussion

Availability and disaggregation of data (reporting and recording)

- It was confirmed that detailed information on programme performance, detection and treatment coverage for XDR–TB would not be available until the launch of the forthcoming global TB report (expected end of 2015). Capacity-building, equipment and consumables were certainly needed, as drug-sensitivity testing (DST) was still very low in the Region, resulting in low detection rates. Concrete data were also not yet available on resistance to the two new anti-TB SLDs (Bdq and Dlm) but were being assessed by a European Centre for Disease Prevention and Control (ECDC) TB working group, with data release expected within the next year (data structure, definitions and variables yet to be confirmed).
- Regarding the separate recording of treatment outcomes relating to resistance to the first-line anti-TB drug rifampicin (R) (RR–TB), as well as those for MDR and XDR–TB patients, it was established that results from so-called pre-XDR–TB patients were not recorded separately.
- DST results data were limited in many countries, whereas prevalence data were more reliable. It was concluded that data management also needed to be improved, particularly in terms of carrying out proper analysis of data resulting from separate cohorts.

Concerns relating to data presentation in the context of transition from the outgoing (2011–2015) TB plan to the incoming 2016–2020 TB plan

- Given the complicated nature of XDR–TB in the European Region and the Region's high resistance levels, it was agreed that the broad target of 20% reduction in MDR–TB prevalence by 2020 was very ambitious, particularly during the current shift from one TB action plan to another. It was questioned whether any evaluation was foreseen of the shortcomings of the outgoing TB plan, to understand why certain targets had not been achieved and to monitor improvements going forward. While partial country-specific specific analysis of shortfalls and challenges to implementation of the outgoing plan had been undertaken, extensive analysis was needed and was indeed on the agenda.
- The closing (2014) data from analysis undertaken as part of the outgoing plan would be available in 2016, and the indicators included in the performance-based M&E framework had been significantly streamlined (from 114 indicators to 24) for the new regional TB action plan 2016–2020. While 10 of the core indicators did not cover MDR–TB prevalence, it was covered within the new plan's full 24 indicators, and the Berlin

Declaration's directive documents continued to be taken into account. The overall structure, logic, baselines and targets were to be presented in the full version of the plan.

- A general concern was raised about the difficulties involved in understanding and presenting the reality of the MDR–TB burden, when approaches to expressing prevalence data varied significantly and did not accurately reflect the burden, particularly in terms of core indicators and in the context of varying DST coverage across countries.

How to introduce the new and repurposed drugs into programmatic use for the treatment of DR–TB patients

Dr Fraser Wares, LDR Unit of the GTB

Dr Fraser Wares gave a process-oriented presentation of the strategic plan for the rational introduction of the new and repurposed Group V drugs, focusing on country-level introduction of Bdq and Dlm. He highlighted that programmatic conditions differed significantly from a randomized controlled trial (RCT); determining which patients should receive the drugs was a difficult decision that needed to be (cost–)effective. Against the backdrop of currently insufficient drug-safety monitoring (DSM) in most TB programmes, extra efforts needed to be made in programmatic terms to introduce these drugs safely and effectively, to ensure they were not lost to resistance. DST was not yet widespread for Bdq and Dlm, for which introducing effective regimens was a key challenge, with country differences across the Region. Dr Wares reminded participants that equitable access to treatment was crucial, along with the need to act quickly, but that patient and drug safety were paramount, as was avoiding resistance. An introduction process differentiated by country context would be needed, along with close collaboration with the relevant partners.

Dr Wares also reminded attendees of WHO's various guidance documents and policy implementation recommendations on the rational introduction of new drugs and regimens. The information notes produced by WHO were essential to communicate the evidence required to drug manufacturers. The standard approach to introducing a new drug was a process of data evaluation and systematic reviews, involving expert consultants from outside WHO, and only then issuing recommendations. This had not been possible in full for Bdq and Dlm, which in itself raised safety concerns over their licensing, and the evidence presented from the drug manufacturers presented a significant challenge for the expert groups to assess the limited data and produce rational recommendations. The benefits of these drugs must be balanced against the amount of detailed background work to be carried out and gaps to be filled to ensure their safe introduction.

In many countries, regulatory authorities also needed assistance. Traditionally it had not been the remit of WHO to work with drug developers, agencies and regulatory authorities, and as such this background work represented a challenge that could not be met all at once, alongside tackling the multifaceted concerns relating to introducing new anti-TB drugs. The task should be broken down into achievable steps, following the approach: "start small, learn, gain evidence, scale-up". Dr Wares reiterated that many questions required answering before programmatic use of the drugs could be implemented, including on matters such as laboratory networks, epidemiological concerns, definitions of all TB forms, R-resistance diagnosis, supply-line issues and importation or customs delays, ADRs (especially with drug-mixing, raising resistance risk) and irrational drug use in countries with large private sectors. Further, he emphasized that without community and civil society backing, introducing these drugs into programmatic use would fail, patients would suffer and the drugs would be lost to resistance.

Dr Wares referred to WHO's *Policy implementation package for new TB drug introduction*[3] as a key tool for supporting countries in preparing to introduce the new drugs, as it contained the steps necessary to decide (and ensure) whether a country was ready. Points explored included:

- the framework for introduction and minimum requirements for country preparedness and planning, including the need for (and how to prepare) an implementation plan;
- the essential nature of active PV and drug resistance surveillance, along with aDSM concerns and cohort monitoring (with a focus on safety);
- the need to work with the private sector to ensure drug safety and efficacy above all;
- difficulties that can arise with regulatory authorities, laboratory structures and procurement mechanisms/lines, requiring a systems-based approach to ensuring uninterrupted supply of high-quality medicines;
- the importance of ensuring adequate financing (for example, with funds from the Global Fund (GF) and/or United States Agency for International Development (USAID), where possible);
- the aim to introduce pilot sites and generate evidence for scale-up into programmatic use of the drugs, including finding and regulating the necessary mechanisms; and
- the scope for continued research to target operational uncertainty, and the need for information feedback to build new policy.

Dr Wares explained that while development of the interim policy documents by WHO had been rapid, once new evidence and data were available and had been analysed, interim guidelines could be translated into recommendations for programmatic use, with updated WHO recommendations on the use of the new drugs anticipated to be available in 2016.

Discussion

- Participants commented on the so-called chicken and egg nature of the problem of introducing new drugs while ensuring no resistance to them; DST was needed on Bdq and Dlm to acquire sufficient data to assure their use, but no validated DST or external quality assessment system yet existed. It was pointed out that discussion tended to centre on how to test Dlm and Bdq, but not the Group V drugs. A large, lengthy study on fluoroquinolones (looking at thousands of specimens across nine countries) was only after many months of work delivering raw data results (due in 2015), highlighting the time lag that existed in obtaining data on which to base further work.
- At field level, a quicker, more pragmatic response was needed, to establish which drugs could be tested and how subsequent capacity could be built. Testing was in reality limited to FLDs; receiving permission from regulatory authorities to test any SLDs was difficult and lack of funding represented a real barrier for many countries. Furthermore, no single guidance package existed for the national reference laboratories (NRLs), resulting in no coordination of what and how they tested drugs. It was expressed that laboratories should therefore be encouraged to test other SLDs, not just Bdq and Dlm.
- Since a key characteristic of XDR–TB patients was their proven resistance to some SLDs, the category of patients known informally as pre-XDR–TB (plus others known to be intolerant to FLDs) were the ones to be considered more closely. The primary concern was not the substitution of a drug or drugs from the optimized background regimen, but rather adding drugs to regimens, to target so-called pre-XDR–TB, XDR–TB and intolerant patients.

[3] Available at the WHO website: http://www.who.int/tb/features_archive/pip_newtbdrugs/en/.

Update on current WHO policy recommendations on the use of new drugs (interim guidance on Bdq and Dlm), Group V drugs and repurposed drugs in the treatment of DR–TB patients

Dr Christian Lienhardt, Policy, Strategy and Innovations (PSI) Unit of the WHO GTB

Dr Christian Lienhardt (attending virtually) spoke of the rigorous process – set out in the *WHO Handbook for guideline development*[4] – undertaken to ensure high-quality standards for evidence-based guidelines, which were then translated into policy recommendations. He reiterated the highly unique nature of the approach WHO was spearheading with these SLDs, in direct response to patient need but without the usual development pathway. He outlined the WHO approach to compiling such guidelines, describing the GRADE process (Grades of Recommendation Assessment, Development and Evaluation) used to assess the quality of evidence available and confidence on efficacy and safety of the drugs, with various categories to indicate the strength of the resulting recommendations (strong or conditional). Dr Lienhardt presented the results of the Phase II data trials for Bdq and Dlm, drawing conclusions on their efficacy and side-effects. For both drugs, safety concerns had been raised, and each had been granted a "conditional recommendation, [with] very low confidence in estimates of effect". The conditions for the introduction of each were similar, encompassing: proper patient selection; informed patient consent; strict treatment regimen design (following WHO recommendations); close patient monitoring; active PV; and management of AEs.

Discussion

- It was confirmed that thus far, no additional or different side-effects had been observed across countries; data showed QT-interval prolongation and hepatoxicity, but not in any country-specific pattern. The profile built did not confirm mortality concerns, which was encouraging, but reporting remained limited (aside from three main cohorts, for which the datasets had been made public). An abundance of anecdotal evidence existed, but not enough data for finely disaggregated safety analysis.
- Concerns were raised about the QT-prolongation side-effects when treating patients with Group V drugs followed by the new SLDs. It was confirmed that as yet no joint use of these drugs had been reported and no toxicity risk assessment data were available on the combination of Bdq and Dlm. **More information was needed on drug combinations, in terms of safety, efficacy and data collection**.
- It was reiterated that the *Policy implementation package* and Bdq implementation plan[5] were essential reference documents to guide countries and assess their readiness to introduce the new drugs. Implementation should not be rushed; background work was needed to establish what mechanisms were already in place, what could be strengthened and what was missing, drawing up an implementation plan using the key guidance and recommendations from WHO. It was emphasized that implementation would look different across various countries, especially as regards active PV levels, with a crucial factor being the country's ability to manage AEs.

[4] Available at the WHO website: http://www.who.int/kms/guidelines_review_committee/en/.
[5] *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance.* Available at the WHO website: http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/.

Update on current overarching WHO programmatic management of DR–TB (PMDT) policies and guidance, focus on overarching PMDT, including recommendations on the use of Group V drugs and repurposed drugs in the treatment of DR–TB patients and ethics and palliative care

Dr Ernesto Jaramillo, LDR Unit of the WHO GTB

Dr Ernesto Jaramillo (virtually) presented an overview of the development of guidelines and assessment of evidence by WHO over the years, now incorporating the GRADE process and resulting in a more comprehensive approach to PMDT today, with a focus on clinical aspects and systematic reviews. He explained how the classification of anti-TB drugs – particularly the repurposed Group V drugs, for which efficacy and safety evidence were neither abundant nor clear – had changed and would change again in the light of new guidelines. The lack of evidence of the effect of Group V drugs (on MDR–TB patients) could be attributed to the fact that treatment was from the outset less likely to achieve cure. It was therefore harder to "move them up the scale and into use".

Dr Jaramillo described how restrictions on Group V drugs varied from country to country. In some places, off-label use was possible under certain conditions but the design of treatment regimens must be done carefully, bearing in mind that country-dependent importation issues were a potential barrier in many settings. He reminded participants of the recommendation in the 2011 guidelines on PMDT[6] that MDR–TB treatment should ideally be carried out in ambulatory care settings, as hospitalization had been found to be problematic in terms of care outcomes and cost–effectiveness. He spoke of the 2015 update of the core and complementary essential medicines list (EML) (19th) and the fact that WHO-backed inclusion of drugs in the list could enable reluctant regulatory authorities to be convinced of the safety and efficacy of the drugs, either adding weight towards a waiver or as a step towards accepting manufacture and registration.

Dr Jaramillo emphasized the importance of infection control in dealing with DR–TB, given the limited treatment options available and limited infection control capacity at individual country level, highlighting the work of WHO in compiling infection control recommendations[7] and the official position update from August 2012, enabling countries to introduce short-treatment regimens. Dr Jaramillo described the ethical, safety and effectiveness, and patient-monitoring criteria required by WHO to allow the introduction of such regimens, along with the need for adequate funding to test the regimens under clinical trial conditions. Broad recommendations from WHO's Strategic and Technical Advisory Group for TB (STAG–TB) had been compiled to provide general strategic advice to the GTB. WHO also supported compassionate use or expanded access programmes for new unregistered anti-TB drugs for use in end-of-life care or where treatment options were severely limited. Pioneer projects by partners such as Médecins Sans Frontières (MSF) had paved the way for wider use, but registration and consideration of legal elements remained key issues.

The *Practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis*[8] outlined the need for proper M&E and assessment of data in order to understand the safety and efficacy of essential anti-TB drugs, requiring specific data collection and analysis approaches to be incorporated into PV, ultimately to improve treatment outcomes. *Guidance on*

[6] Available at the WHO website: http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/.
[7] Available at the WHO website: http://www.who.int/csr/bioriskreduction/infection_control/publications/en/.
[8] Available at the WHO website: http://www.who.int/medicines/publications/pharmacovigilance_tb/en/.

ethics of TB prevention care and control[9] was another document produced by WHO. Dr Jaramillo emphasized that ethical considerations regarding (for example) monotherapy, patients that remain contagious, or action to protect health care workers in contact with TB, must be taken into account in each country setting. He highlighted the importance of the *Patients' Charter for Tuberculosis Care*,[10] which was in the process of being updated in the context of the new TB strategy (2016–2020), with heightened coalition between partners and donors. The roles, rights and responsibilities of patients and the underlying goal of zero patient suffering remained very much relevant today.

Other guidance documents mentioned included the International Standards for Tuberculosis Care (ISTC), looking at the available evidence and recommendations for the management of MDR–TB through a coalition of partners and societies (including in the private sector), combined with WHO action to ensure: timely and accurate diagnosis; standardized, effective treatment regimens; appropriate treatment support and supervision; informative M&E; and a responsible public health response. Dr Jaramillo reiterated the importance of WHO's *Companion handbook* (revised in 2015 to include Dlm use in TB care) as an essential reference document to inform local good practices, drawing attention in particular to chapters covering patient-centred care, social support and treatment adherence (a crucial component of the new TB strategy), and palliative care. This was important in the context of the (albeit small) number of patients without treatment options and the fact that DR–TB still has worse survival rates than many cancers. Programmatically, it was necessary to consider not only that these patients suffered and many died, but also that they were still transmitting TB while doing so. Palliative care must therefore be strengthened alongside proper infection control measures.

Discussion

- Training governments on the complex (ethical) issues involved in prioritizing patient entry into new drug treatment programmes was necessary to allow more constructive interaction with WHO and movement towards programmatic management of the introduction of the new drugs. It was explained that WHO collaborating centres (CCs) were working in key areas to counter the problems related to increased population life expectancy and the resulting suffering, as well as gaps in care.
- The fact that palliative care was already stigmatized was discussed, particularly when limited or no treatment options could be offered to the patient. However, infection risk and control issues needed to be considered alongside ethical duty-of-care issues (because TB infection risk continued in palliative care, unlike in the example of cancer, which was noncommunicable), to assure quality of life and take into account public health concerns. Unfortunately, aside from countries' own (government) funding, palliative care financing was not known to be available from donor organizations, and technical agencies and partners were struggling to find external funding for end-of-life care.
- A concern was raised about the clear lack of communication regarding the various approaches to funding palliative care employed in other regions, where funding streams were known to be available and where end-of-life care was seen and understood as being very much part of TB care, including from the point of view of ongoing infection control. Sharing experiences and approaches was essential, along with clearer lines of communication.

[9] Available at the WHO website: http://www.who.int/ethics/publications/9789241500531/en/.
[10] Available at the WHO website: http://www.who.int/tb/publications/2006/istc/en/.

Safety monitoring of drugs used to treat DR–TB patients

Dr Dennis Falzon, LDR Unit of the WHO GTB

Dr Dennis Falzon (virtually) presented the basic principles of TB drug safety management and monitoring, discussing the essential nature of patient safety – from both patient health and health system perspectives – in view of the problems associated with ADRs. He also outlined the key challenges for TB patient safety, including: off-label use; the conditional approval of new MDR–TB drugs; the unknown risks of new drug combinations; the costs associated with detection and management of ADRs; and the potential effect on public confidence and national TB programme (NTP) credibility in countries. Dr Falzon presented the WHO definition of PV, emphasizing the need for prevention of AEs and for active monitoring to be prioritized over spontaneous or targeted reporting. He provided details of this active approach to PV, including: additional tests and patient questioning; assessing potential AEs and screening of patient records; and the need for a prospective format to reduce bias and assure reliable data. Such a method would allow follow-up to continue after treatment ended and AE reporting to focus on actual episodes rather than known reactions or pharmacology-based expectations. Dr Falzon explained that a cohort approach to aDSM would be the most suitable, fitting the framework that was familiar to NTPs in order to monitor treatment responses and react rapidly: aDSM should lead to action for the benefit of individual patients, as well as national and international policy-making where possible.

Dr Falzon went on to explain resources available on PV and aDSM, including ongoing work and publications produced by WHO and the Global Drug-resistant TB Initiative (GDI) and various online resources. He reviewed WHO's advice to countries (from 2012, since adopted by other partners) on ethical review, active PV and patient monitoring in shorter regimens for MDR–TB, outlining that further discussions between technical agencies had taken place in July 2015 in Geneva, which had established various needs to be fulfilled to further aDSM and PV work (including the need for a global database for aDSM data to aid PV efforts and a plan to improve competence in aDSM methods by training and mentoring). Dr Falzon presented the features and a sample schematic for aDSM, including detailed steps for defining and organizing the cohort in order to test patients, manage data, communicate results and scale-up to an effective PV system. He outlined eight key steps for aDSM implementation, with two key areas of focus: standardizing data collection and proper staff training. He also highlighted the necessity and functions of an aDSM steering group. Immediate uses of the data were also presented and the necessary local adaptations discussed, along with a useful flow diagram to show how the NTP should feed into the national PV system.

In conclusion, Dr Falzon reminded participants that DSM was a relatively new area of work, development was slow and challenges remained in terms of terminology, testing (type and intensity), data collection, consolidation, analysis and reporting (national and global). Countries needed help with implementation, specifically in terms of AE management, defining how to link records for signal detection and contributing to global monitoring. In order to make aDSM a standard component of MDR–TB care, fresh resources (both domestic and global donor funding) would be needed. The requisite parameters for aDSM would be shared by early 2016, including a training plan.

Discussion

- It was explained that country-specific spontaneous reporting forms were formatted differently to the AE checklist form described for aDSM, as baselines and measures were

slightly different. This still constituted event (or episode) reporting, just shorter and with a different intention.

- The distinction was drawn between AEs, which could be any untoward effect or harm noted, possibly associated with a drug used in treatment (no association required in order to call it an AE) and aDSM. Unexpected events could also be recorded within aDSM, but the unit/trigger for PV reporting was the AEs themselves, namely, serious AEs during treatment or follow-up that involved hospitalization or were life-threatening (rather than strict, broad-scale event monitoring that took into account every event). It was confirmed that increased emphasis was now being placed on serious adverse events (SAEs), with the spectrum of intensity moving away from active PV cohort monitoring and closer to an aDSM monitoring model, targeting specific life-threatening AEs and side-effects. Updated guidance on PV and aDSM would be available in autumn 2015.
- In discussion of the role of the WHO CC dealing with passive PV in Uppsala (Uppsala Monitoring Centre), it was clarified that since mid-2014 the centre was no longer involved in TB cohort event monitoring and as such alternative partners and funding were being sought.

Update from the European rGLC Secretariat

Dr Martin van den Boom

Dr Martin van den Boom described the picture of the global and regional TB burden, highlighting the unequal distribution of MDR–TB among the countries of the European Region. He gave a brief overview of the key focus areas for the rGLC Europe, including:

- boosting the safe, rational introduction of MDR/XDR–TB SLDs, working with all partners involved;
- fostering collaboration through joint workshops (including virtual ones) and encouraging partners to present at these events alongside rGLC members;
- collecting models of care and advocating for expansion of MDR–TB treatment on an ambulatory basis, to help countries replicate this in their country contexts;
- continuing to assist with updating of infection control national plans for inpatient and outpatient facilities;
- supporting Member States to adapt the new regional TB action plan and implement and update their national strategic plans, focusing intently on PMDT aspects;
- helping to strengthen surveillance capacity in countries, aiming to ensure reliable recording of MDR–TB figures;
- engaging in operational research, leading to more efficient care models and reduced treatment duration;
- supporting the mentorship programme, moving graduates on to specific missions and renewing regional capacity to meet the technical assistance needs of individual countries; and
- tailoring terms of reference (ToRs) for technical assistance missions to ensure the various country-specific financing and health system strengthening needs are met (requiring flexibility).

Dr van den Boom explained that an external analysis of recent years' GLC reports was under way (to be finalized by December 2015) to establish what had (and what had not) been implemented successfully at country level in previous years, obviously with a view to improvement.

The Chair officially welcomed Dr Masoud Dara, who expressed appreciation at such high-level attendance of the workshop. He reiterated that 48% DR–TB treatment success was far too low and that having to wait three years (or more) for outcomes was too long. The GLC was simplifying the process to understand the data, but the lack of a systematic data collection process across countries, poor adherence to treatment regimens, DST coverage issues and even resistance itself were all significant problems remaining to be overcome. As such, Dr Dara encouraged participants to think of the workshop as a call for lateral thinking to those working directly in the field, reiterating the need to extract learning points from the event by identifying changes needed to bring about improvement.

Update from the Global Drug Facility (GDF) on Group V product availability, policy to access these drugs and updated prices

Mrs Nigorsulton Muzafarova, Stop TB Partnership Secretariat GDF

Mrs Nigorsulton Muzafarova gave a detailed presentation of the GDF and its activities. The partnership was no longer hosted by WHO, but was in the United Nations Office for Project Services (UNOPS). Its main focus was expanding access to quality-assured drugs (FLDs and SLDs) and diagnostics, while contributing to the development of sustainable procurement and supply management for countries in need. She outlined the GDF's strategic objectives and key policies, including the general conditions for providing assistance to countries, the procurement process (drugs are supplied through a contracted procurement agency), monitoring and technical assistance missions (prioritized according to issues reported), and special provisions for group V medicines (including ADR reporting, use of off-label products, endorsement from NTPs and liability waivers).

Mrs Muzafarova explained the special process in place for Bdq-related policy, which includes: encouraging use of the Bdq donation programme available through USAID; resolving country-specific issues to ensure programme eligibility; and providing technical support to countries to ensure they met the five key WHO recommendations for Bdq introduction. These included:

(1) close monitoring of treatment according to protocols and guidelines for managing patients with DR–TB;
(2) using a patient inclusion mechanism, allowing proper review of patients waiting to receive Bdq by a specialized team (consilium/committee) and requests for technical assistance to be submitted;
(3) obtaining informed patient consent;
(4) adhering to the principles outlined in the *Companion handbook* of designing a DR–TB treatment regimen; and
(5) carrying out PV and proper management of ADRs.

Mrs Muzafarova outlined the steps that must be included in preparing the Bdq implementation plan, including carrying out the requisite data analysis to estimate the number of patients who will benefit from the drug (as only countries with the right plan arrangements in place would be granted the drug, and then only for eligible patients). This latter procurement step required extensive data review, taking into account scale-up plans and the drug's 24-month shelf life. Further stages included reviewing the need for other Group V drugs (SLDs) to treat patients receiving Bdq and ensuring the technical assistance needs had been understood and communicated to GDF and USAID. Mrs Muzafarova emphasized strongly the need to place the order for Bdq and other SLDs well in advance (once all conditions were in place), because the lead time was likely to be several months. Technical assistance activities could take place while

awaiting drug arrival, however, including: seeking funding (for example, re-programming GF financing to introduce new technologies); developing the mechanism for importing Bdq (usually via an importation waiver) where one did not already exist; and reviewing clinical cases and patient histories to establish which patients could benefit from Bdq in their treatment regimens (such as those currently failing DR–TB therapy, those with resistance to fluoroquinolones or injectable SLDs and those having experienced AEs). It was important to note that although the USAID donation programme had committed to funding the drugs and providing technical assistance (which could be requested for any or all areas of Bdq introduction), countries would still need to account for procurement-associated costs, including, but not limited to, freight, quality control and inspection, and insurance.

Mrs Muzafarova described the formulations of Group V drugs available, detailing sources of certain drugs and outlining some supply problems that had arisen. She wanted participants to understand that until there was adequate evidence of demand for a certain drug, it would not be supplied or justified for inclusion in the list; that is, a direct link existed between (justified) demand and supply, compounded by the added problem that bioequivalence testing was still needed for some drugs. Mrs Muzafarova detailed access to Group V drugs by WHO region, showing that Europe was leading in terms of ordering and treating DR–TB patients with Group V drugs, and she confirmed that countries could apply for more Bdq than originally requested as part of the donation programme, should they discover more was needed.

Mrs Muzafarova outlined the costs of key products and explained that further price reductions were expected (where competition allowed) during the next tender, but significant cost reductions were difficult to achieve, given the low uptake of most Group V drugs. To address lead time issues, the strategic rotating stockpile (SRS) of drugs had been increased (to 12 500 patient courses) and the list of products included in the SRS increased, including injectable anti-TB drugs and Group V drugs (since 2014).

While risky to include and costly, Bdq was also being discussed for inclusion in the SRS. One concern was the off-label use of certain drugs (such as clofazimine (Cfz)), where orders had been delayed owing to importation issues or customs clearance, having knock-on effects resulting from the drug's short shelf life, as well as the fact that it was not included on WHO's EML. Off-label products were very useful in anti-TB treatment but strong WHO recommendations were needed to convince regulatory authorities of WHO endorsement and encourage their use.

Other issues included the fact that there was only one qualified supplier for some drugs (again, Cfz, for which Novartis was not participating in tenders), and the supplier was not meeting GDF's quantity needs, despite the demand being clearly expressed. Discussions were underway with other partners/suppliers but no resolution had been found as yet. Low demand, slow implementation plan development, limited manufacturers (for drugs like linezolid and clofazamine) and high minimum order quantities and prices presented further barriers to introduction of the drugs in some countries, with long lead times being the most significant concern (especially for Bdq). Ensuring the drugs entered countries with sufficient remaining shelf life was even more problematic when the demand was low (as in the case of linezolid (LZD), impacting on cost–effectiveness.

Discussion

Technical questions relating to drugs (dosages, supply chain, etc.)

- Mrs Muzafarova explained that LZD was only available currently as a 600 mg dose tablet. Meropenem was not available at all through the GDF, and lead time for Bdq was longer than the usual GDF six months of ordering, but the GDF was unable to do anything to influence this lead time as the manufacturer only made a limited number of courses in batches according to its own manufacturing schedule. Discussion was therefore needed to encourage countries to split deliveries to avoid problems with the remaining shelf life when a batch becomes available; however, countries were reluctant to split deliveries on cost grounds and ongoing frustrations with long importation processes and customs delays. A suggestion to alleviate this was for rGLC to work with individual NTPs on proper planning and staggered deliveries.
- Technical issues regarding supply and transport of Bdq were discussed, relating specifically to patient movement and various facilities using different administration routes. Mrs Muzafarova confirmed that no other packaging options (only jars) were available for Bdq at present (although the manufacturer had been informed of the preference for blister packaging in future), with a strong recommendation against opening, splitting and storing the dosage owing to limited stability data (drug stability was only assured in room controlled temperatures and conditions).
- Additional stock requests (owing to, for instance, damage and loss) were discussed as an area of concern. Technical guidance was requested on how to proceed in terms of the ethical questions raised by using two different batches of Bdq with similar expiry dates in a treatment regimen over a period of full treatment through various supply mechanisms (such as donation programme). Mrs Muzafarova's advice (on which she would seek clarification from the USAID TB Team) was to minimize waste, as Bdq was a very expensive drug, and to follow the general principle of using first the drug with the shortest expiry date.
- Regarding partial procurement practices, whereby FLDs were procured through government funds but donor funding was being used for the procurement of SLDs, Mrs Muzafarova stated that discussion with the GF and other partners to push for use of quality assured products only were ongoing. Quality of drugs (and therefore treatment) was paramount and if governments procured drugs from more than one source, and/or countries implemented drug use differently, and/or patients changed products, the resulting quality issues could lead to drug resistance (obviously to be avoided at all costs). The aim was always to use only quality-assured products to maintain treatment success rates.

Ethical and legal considerations

- One manufacturer's approach to supplying new drugs was raised as a serious concern, as the company required access to patient lists (including names) before agreeing to supply SLDs. Ethical considerations aside, patients were put at very real risk of dying while the resulting administration process was resolved. Mrs Muzafarova assured participants that to the greatest extent possible, the GDF would negotiate to ensure patient confidentiality. It was explained that the standpoint of the manufacturer in question had in fact relaxed from an initial position of much more stringent controls (any patient receiving Cfz previously required a prescription signed by a Swiss-accredited physician), so patient confidentiality in this context was a necessary compromise to allow Cfz (in this case) to be used in anti-TB treatment where needed.

- It was agreed that the strict "hoops to be jumped through" required by manufacturers were compounded by delays in the administrative process for the drugs to enter countries legally, as the documentation accompanying the drugs did not always tally with the point of origin or destination and import could therefore be stopped by the regulatory authorities. The point was raised, however, that this did not always happen: that is, in some places the drugs got through by means of "some loophole or other". This inconsistency resulted in a lack of understanding among countries (and indeed, technical support personnel). As such, the whole process needed to be clarified, working with countries within and around the restrictions to ensure a smooth supply of quality-assured drugs for the sake of patient safety.

Perspectives on the introduction and access to new drugs for DR–TB treatment, and an update on the Bdq donation programme and its coordination with other partners and programmes

Dr Sevim Ahmedov, USAID TB Team (Bureau for Global Health)

Dr Sevim Ahmedov thanked the rGLC members for their work with individual countries, citing them as an example to other similar regional initiatives. He outlined the memorandum of understanding (MoU) signed between USAID and Janssen on 11 December 2014 and the Gift Agreement that followed in March 2015, with the donation programme starting in reality in April 2015. The donation programme was available to any country, provided the funding and the drug supplied were used appropriately in accordance with WHO guidelines. The idea was to remove the price barrier for countries and gather evidence on the use and impact of Bdq to facilitate the scaling-up of treatment for MDR–TB. He reminded participants that additional gift funds were available from Janssen where needed and that the manufacturer was also prepared to provide documentation, medical information, and/or education to assist countries and individual programmes to implement use of the donated Bdq. The operationalization of this was to be determined by the workshop participants in the course of their work with specific countries on introducing new TB drugs.

Dr Ahmedov emphasized that the eligibility criteria for the donation programme were broad – if the country had been eligible for GF financing, it would be eligible to receive donated Bdq, provided it met all five WHO conditions set out in the *Interim policy guidance on the use of bedaquiline in the treatment of MDR–TB* (effective treatment and monitoring system in place, proper patient inclusion criteria, informed consent, adherence to WHO PMDT recommendations and active PV and aDSM in place). The donation must also be in compliance with local laws and regulations and countries must agree to: provide forecasts to Janssen; take responsibility for all storage, transportation, delivery and safe destruction of the drug in compliance with the requisite good distribution practices; and report any AEs or special situations that arise during treatment.

Dr Ahmedov discussed the current status of Bdq orders (25 countries thus far) through the donation programme, admitting that while faster uptake would be nice, the bigger picture needed to be clarified for countries in terms of how to introduce and manage the drug if they were to receive it. Nigeria was given as a good example moving forward, having put Bdq on their EML, which would encourage other countries that were watching carefully the development process. He outlined the common barriers to receiving Bdq donation, including: the additional burden and complication experienced by countries that were already struggling with PMDT implementation; lack of funding; low numbers of patients; and reluctance to introduce new drugs until more safety and efficacy evidence was available (among other local regulatory problems or country-

specific political issues). Dr Ahmedov stated that an active approach to Bdq introduction was being implemented for most high-burden MDR–TB countries, with assistance provided by USAID and technical partners to help countries overcome barriers to inclusion in the programme and strengthen capacity for PMDT. Help would also be given to identify and access any other external support available, including working through the four key pillars for the introduction of Bdq (DST testing and drug-regimen design, clinical monitoring, PV, and supply and medicines management), technical assistance with drug ordering and continued support throughout programme implementation. Dr Ahmedov directed attendees to online Stop TB GDF resources[11] and the drug procurement form that could be found there as a starting point for considering application to the donation programme.

Discussion

- In discussion of who was responsible for the extra associated costs (storage, transportation, etc.) if the drugs (but only the drugs) were funded by Janssen through the USAID donor programme, Dr Ahmedov reiterated that these additional costs were definitively not USAID's responsibility. The drug (only) was provided at no monetary cost, but with certain expectations in return (AE reporting and patient monitoring, regular forecasting, responsibility for delivery, proper handling procedures, and so on). All other costs were the country's responsibility (often achieved through GF financing or the respective government's own funds) and help was available to identify funding mechanisms, as well as technical assistance with planning, budgeting and re-programming funds from elsewhere.
- Regarding the scope of AE monitoring within the requirements of the donation programme, Dr Ahmedov stated that USAID's position was that cohort monitoring would remain the ideal, but provided AEs were reported, agreements could be reached and arrangements could continue. It was further discussed that ideally countries should not have to choose whether to first implement a working PV system or start treating patients – treatment was needed, as was adherence to treatment regimens (equally). As the patients took the drugs, so the data would be collected. Dr Ahmedov agreed, but stated that some countries needed evidence and experience from others to reassure them before being prepared to join the donor programme. The general principle was to work together to iron out the details and the expectation was that workshop members would be key to taking forward this work.
- Dr Ahmedov reiterated that where funding mechanisms were not available or countries had not planned their public sector budget well enough in advance to cover the additional responsibilities involved in acquiring Bdq, USAID would work with them to explore financing options and provide technical assistance for forecasting, among other things. The right time to consider this was when (or even before) countries considered ordering the drugs.
- It was also agreed that work must be carried out with countries to find a programmatic or operational solution to the logistical problems that were creating barriers to more widespread uptake of the donation programme. USAID and technical partners could help by bringing so-called clout to the process, using their influence to establish which resources were available to countries and how to access them if the information was to be shared in a timely manner across the board. Coordination, communication and planning were key.

[11] Available at the Stop TB website: http://www.stoptb.org/gdf/.

- A practical approach to data analysis was needed in terms of identifying patients who would benefit most from treatment with Bdq. This involved "cleaning" (that is, triage of) the cohort so that only those patients who did not require a 20-month regimen were left; these would be ideal for shorter treatment regimens. The point was to plan for implementation, helping countries to write long-term plans that would enable more widespread uptake of donor programmes such as USAID's. Planning (including planning to use expensive drugs) was the key to lower drug costs, and the key to extrapolating the necessary information was to identify so-called pre-XDR–TB cases first. Modelled calculations could be made for cohort cleaning (as examples of shared good practice), so that participants could triage patients according to their needs.

Session 2. Objective: to share experiences of countries, rGLC members and partner organizations (technical and donor) that have introduced or supported the introduction of new and/or repurposed drugs into the treatment of DR–TB patients

The experience-sharing template given to presenters is shown at Annex 4.

Experience-sharing: Republic of Moldova

Dr Kai Blöndal, rGLC Europe member

Group V drugs and laboratory capacity

- The Republic of Moldova had recently updated its MDR–TB guidelines and national TB programme (the latter not approved yet by the Ministry of Health). In terms of laboratory capacity, Dr Blöndal presented detailed information on which diagnostic methods were available and in operation in the country.
- A two-year clinical trial of Dlm in the country had ended in 2014, but as yet treatment outcomes had not been reported. In 2015, amoxicillin plus clavulanate (Amx/Clv) and imipenem plus cilastatin (Ipm/Cln) were procured for 14 patients, along with LZD for 30 patients. In 2016–2017, several Group V drugs were to be introduced with funding from the GF and Bdq was to be introduced under the USAID donation programme, with a plan to scale-up treatment progressively each year (patient numbers were 16 in 2015, 38 intended in 2016 and 36 in 2017).
- Treatment regimens were implemented as per national guidelines. The country's figures did not include so-called pre-XDR–TB patients.

PV

- The Republic of Moldova had a national PV system and capacity to record individual side-effects and ARs on specific forms in patients' files. However, doctors were not diligent at reporting and cohort AE monitoring was not carried out.
- The country was a partner of the Uppsala Monitoring Centre and TB drug safety, management and monitoring measures were in place at TB programme level. Planning to implement these elements at national level had begun, but it would take time.
- There was room for improvement in all areas of PV and DSM. Analysis of side-effects and ARs was carried out at national level.

Country- or project-level policy related to the introduction of new anti-TB drugs

- A legal framework existed for the introduction of new drugs for DR–TB treatment, along with importation waivers. The system should be sufficient, but was not efficient, with long delays and much bureaucracy.
- The country had access to international (WHO) policy documents, but using English-language documents was a problem: they needed to be translated into Russian and Moldovan, as there was a strong preference to use only nationally approved guidelines, causing delays while updating recommendations based on new evidence (and translating them).
- Several items were identified as essential for addressing the challenges to sustainable introduction of new/repurposed anti-TB drugs, including:
  - training of clinicians and nurses;
  - gathering clinical experience by means of a pilot programme/site; and
  - introducing all issues described into the national implementation plan for the introduction of the new drugs (in particular recording, reporting and monitoring issues).

Experience-sharing: Tajikistan

Dr Kai Blöndal, rGLC Europe member

Group V drugs and laboratory capacity

- Doctors were happy with treatment outcomes thus far of patients receiving Group V drugs in Tajikistan. From 2014, Cfz, LZD and Amx/Clv have been available to paediatric patients and their relatives (under an MSF initiative). In 2015, Bdq was procured with help from MSF for at least five patients and 30 patients received LZD with GF support (with MSF donations of Cfz and Amx/Clv for those patients on LZD). From 2016, several Group V drugs are planned to be introduced with support from the GF and Bdq is to be introduced under the USAID donation programme. No time frame was known for Dlm procurement.
- In terms of laboratory capacity, Dr Blöndal provided information about which diagnostic methods were available and in operation in Tajikistan.
- It was difficult to predict the number of patients for treatment and, as such, the process for doing so was under revision. The GF had been advising during the grant application preparation process to show an increase in cases in general, "trickling down" to arrive at the number of MDR/XDR–TB patients. However, this was not found to reflect reality, given the actually decreasing number of TB and drug-resistant TB cases and case notification difficulties in the field. Grant budgets were therefore prepared for a wider range of (or more) activities, and countries were now realizing they would not diagnose so many patients (even using GeneXpert (properly)). The budget was therefore being revised on that basis and concerns over lack of data fidelity would hopefully be eliminated with the next round of data.

PV

- Tajikistan had a national PV system and capacity to record individual side-effects and ARs on specific forms in patients' files, but doctors were not diligent at reporting and cohort AE monitoring was not carried out.
- The country was partnered with the Uppsala Monitoring Centre. TB drug safety, management and monitoring measures were in place at TB programme level; planning to implement these elements at national level had begun, but this would take time.

- Room for improvement existed in all areas of PV and DSM. Analysis of side-effects and ARs was carried out at programme level in Tajikistan, covering mainly patients hospitalized in the Macheton Hospital.

Country- or project-level policy related to the introduction of new anti-TB drugs

- A legal framework existed in Tajikistan for the introduction of new drugs for DR–TB treatment, along with importation waivers. The system should be sufficient, but was not efficient – long delays existed, along with too much bureaucracy.
- Access to international (WHO) policy documents was possible, but the documents needed to be translated into Russian (and, if possible, to the Tajik language) as use of English language was problematic on various levels. Nationally approved guidelines were required, causing delays while updating recommendations based on new evidence (and further delays in translating them).
- Several items were identified as essential for addressing the challenges to sustainable introduction of new/repurposed anti-TB drugs, including:
  - training of clinicians and nurses;
  - gathering clinical experience by means of a pilot programme/site; and
  - introducing all issues described into the national implementation plan for the introduction of the new drugs (in particular recording, reporting and monitoring issues).

Discussion

Effect of the change of role of the WHO CC for PV in Uppsala (Uppsala Monitoring Centre)

- Given that the centre was no longer the WHO CC responsible for PV, it was explained that data management had become a matter of sharing, not just collecting. In some cases, MSF would be involved in data management where Uppsala had been previously, but the picture was unclear for some countries. It was further clarified that in terms of the programmatic use of the new drugs, the flow of information would continue from the national level (NTP) to the national PV centre and that the PV centre should still share and exchange information with the Uppsala Monitoring Centre (as was currently the case). The Uppsala centre would therefore be continuing its PV responsibilities, but no longer in its former capacity as the lead agent for TB-related PV in individual countries.
- It was agreed that the working relationship needed to be strengthened between the NTP and the level at which PV takes place in each country. A question for consideration by the attendees was whether a global-level (overarching) TB-specific intervention approach (perhaps in the form of a shared database) was needed between the Uppsala Monitoring Centre (which had essentially moved up one level) and the national PV mechanism. The national PV centre in individual countries should ideally be the facility to signal TB cases and analyse causality – these tasks would not automatically be expected of the NTP. To keep the issue grounded at the patient level, it was necessary to ask how a country intended to identify a rare but potentially fatal reaction among a small number of patients and, further, who (and at what level) would be responsible for coordinating these endeavours (without doubling efforts). The WHO headquarters TB Programme would take responsibility for helping to rebuild country systems around the more limited remit of the Uppsala centre.

How to ensure a cohesive PV system, differentiated by country

- Most countries had no capacity for reporting. Where PV centres existed, they did not function well, and no support was currently available for national entities. Systems-level thinking about monitoring and management of side-effects was a new field for many countries, and they welcomed working with a TB programme to see examples of how to proceed. They needed help to build capacity, not only to mobilize resources. Contrary to the view expressed that "nothing was happening", it was suggested that people and partial systems were simply working in silos. People working in the TB field did have experience of PV cohort monitoring and national-level causality analysis did indeed take place; help was needed to develop and sustain dialogue between the levels of the system and across silos, developing and strengthening links between PV experience and side-effects monitoring. It was suggested that Bdq introduction could be the catalyst for system-wide developments, supported by the WHO TB Programme.
- Capacity-building was understood to be an enormous body of work in which the NTP would need to share, with WHO technical assistance. Personnel working in PV specifically should be invited to working groups and committees, alongside drugs agencies, to facilitate understanding between PV actors. Georgia was cited as an example where this was starting to work well.
- "All kinds of help" was needed to further PV in countries (in Tajikistan in particular). This could be broken down concretely by compiling an implementation plan for the introduction of the new drugs, detailing the needs, responsibilities and areas of weakness in a step-by-step approach. The body or group responsible for such a plan would vary by country, but it was more a question of who would take charge to form the necessary partnerships than how to fund developments, since funding for implementation categorically did exist.
- As PV was relatively new, the concern was expressed that such discussion of it – as though it were possible to cure TB through PV – could be dangerous. The shortcomings of the drugs were not yet known, treatment regimens (where they existed) were not perfect and it was already recognized that patients would default from treatment, leading to resistance concerns. It was important not to move focus away from enabling factors or concentration on patients and treatment adherence. Participants agreed that many factors were (and needed to be) involved in the fight against TB, not least patient treatment adherence. However, this needed to be in combination with PV, not prioritizing one approach over another, and prioritization of these issues by country would be best, rather than aiming for a one-size-fits-all approach. PV made sense for monitoring large cohorts, but for small groups of (20–30) patients, PV was carried out to no effect for the greater good. More guidance was needed on which aspects to concentrate on as countries approached the introduction of new drugs, depending on their programme- and system-specific contexts. It was also important to differentiate between countries in terms of the earlier discussion of which was to come first – a PV system or the introduction of Bdq treatment – without forcing any country to start from one or the other perspective.
- The tendency to dismiss the idea of aDSM and PV before they had been properly tried and the capacity of the results understood was cautioned against, and participants were reminded that it was not yet known how toxic these drugs were, given that many countries did not (yet) collect DSM data. The programmatic introduction of the new and repurposed Group V drugs was the impetus required to set up monitoring and safety systems properly and to ensure data verification. Effective systems were needed not only to record the data, but also to treat patients, which would in turn lead to better outcomes and patient-centred health care systems (which was surely everyone's ideal). While the strategies discussed seemed to create further problems, the intention was that once

operational, they could save lives. The wider aspects of the necessity of aDSM must therefore be considered, at exactly the level of the present workshop.

Experience-sharing: Azerbaijan

Dr Elmira Gurbanova, Project Director for the GF's TB Project Implementation Unit in Azerbaijan and consultant to the rGLC

Group V drugs and laboratory capacity

- Group V drugs were to be introduced in Azerbaijan from 2016, with (USAID donation programme) Bdq introduction and Cfz, LZD, Ipm/Cls plus Amx/Clv under the new funding model for GF support. Dlm procurement intentions were unclear but a short-term pilot project for Cfz had been carried out in 2007–2008 in prisons (with support from the International Committee of the Red Cross).
- A pilot project for new drug introduction was planned for 2016–2017, including 272 patients treated across 24 months, with treatment variations according to TB form and presence of resistance to various drug combinations.
- An implementation plan was also in progress, to be approved in the coming months.
- In terms of laboratory capacity, detailed information was provided about which diagnostic methods were available and which were in use, with variations between NRL and prison laboratories. Details were also provided on DST levels and techniques in both laboratories.

PV

- A system existed for recording individual side-effects and ARs in patients' files, with analysis of these effects being carried out at programme level for patients in prison.
- A PV centre existed at national level under the Ministry of Health and guidelines had been approved and standard forms developed on how to carry out PV activities. However, gaps in capacity and training were evident and technical assistance was needed to improve the national PV system, particularly in terms of cohort event monitoring. Furthermore, protocols needed to be developed, standard reporting forms adopted, ethical committee approval ensured and a data management system established. More help was required from external partners to help close the gaps in knowledge and capacity for dealing with the introduction of new anti-TB drugs.

Country- or project-level policy related to the introduction of new anti-TB drugs

- The legal framework existed for introducing new TB drugs and importation waivers were possible, but the process was lengthy. The existing mechanism was sufficient, but not efficient, resulting in long delays and too much bureaucracy.
- International (WHO) guidelines were available but they were a lengthy challenging process to implement, owing to the lack of English-language understanding in Azerbaijan and a reluctance to use anything other than approved protocols (in Azerbaijani). Having WHO guidelines in Russian may speed up the process of new guidelines adoption (as is the case in other post-Soviet Union countries, Russian is widely used).
- Several essential items were identified to address the challenges to sustainable introduction of new/repurposed anti-TB drugs, including:
  - training of clinicians and nurses, as well as national PV training;
  - launching a pilot programme/site; and

  - introducing the elements described in the national implementation plan for the introduction of the new drugs (in particular recording, reporting and monitoring issues).
- As was the case with the Republic of Moldova and Tajikistan, support was needed in all areas to enable introduction of the new and repurposed Group V drugs.

Discussion

The need for Russian-language policy/guidance documentation

- The need was reiterated for Russian-language translation of international guidance documents to use in countries. Russian translations were underway for some guidance documents (such as WHO's *Policy implementation package for new TB drug introduction*), but others were awaiting updates before translation began (such as the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*, revised in 2015).
- Concern was raised over the quality of centralized and commercialized language translation at WHO. It was felt that errors were creeping in and this could lead to confidence in the documents themselves being shaken. It was agreed that feedback would be passed to the WHO Regional Office for Europe regarding: (a) the need for translation of all policy/guidance into the core United Nations languages; and (b) the concerns over translation quality.

DST in laboratories

- It was explained that in order for clinical management and the quality of DST results quality to improve in the NRLs, dialogue and open relationships must be established with countries with a view to encouraging testing of all drugs intended for use in anti-TB treatment, as well as resolving problems that might arise with certain drugs or tests. Results were already good and quality assurance was possible for fluoroquinolones and SLDs.
- Regarding DST in the NRLs, a discrepancy was raised between the guidance from the WHO Global Laboratory Initiative, which recommended not relying solely on testing as national methods may not be rigorous enough, and the treatment recommendations, which provided specific guidance on adjusting drugs and treatment regimens for MDR–TB patients. Guidance in general on DST was therefore contradictory and difficult to interpret, particularly in light of differing country situations and patient-specific requirements. It was not well understood what the results of DST actually meant, but as a counterpoint it was expressed that communication with clinicians was important to understand the conditions in which resistance had developed. It was reiterated that the guidelines existed to deal with reality and that it was very difficult to identify a so-called gold standard for these drugs. Technical problems already existed in terms of: techniques to identify mutants; data on which critical concentrations were based (and thus lack of certainty regarding DST); and how to be certain of the presence or absence of resistance.
- It was known that many strains of resistance existed, so one question raised was why para-aminosalicylate sodium (PAS) resistance in particular had not been identified. Testing was required for <u>all</u> Group V drugs, so one suggestion was for working groups and laboratories to carry out small studies to identify resistance (or lack of it) to certain drugs. Clinical data needed to be built up, along with assurances that concentrations were correct. It was agreed that strategy was important in this context; that is, not to rely solely on DST, but rather to encourage doctors to use DST information and the guidelines

together to safely add or remove drugs from treatment regimens according to the recommendations.

Experience-sharing: Latvia

Dr Vaira Leimane, WHO CC for Research and Training in Management of MDR–TB in Latvia and consultant to the rGLC

Group V drugs and laboratory capacity

- LZD had been procured by the Latvian Government since 2010 (in increasing amounts each year). Cfz was not available at all in Latvia but was certainly needed. Compassionate use of Bdq had existed in the country from 2013 to 2015 (for 35 patients, all of whom had benefited from its use) and from April 2015 it was to be procured by the government for 10 patients, along with Dlm for 10 patients (since 2014, Dlm had only been available as a (small) donation by Otsuka).
- Dr Leimane described the diagnostic and treatment pathways, regimens and results for MDR/XDR–TB patients, who were often sensitive to the drugs available. Patient history of treatment and testing were taken into account, alongside DST, in order to determine resistance and further treatment possibilities. Increased levels of adjuvant surgery were also having an impact on treatment levels using the new drugs.
- In laboratories, BACTEC/MGIT were available for RR–TB and MDR–TB testing (in use selectively since 1998 and for all patients since 2004). Solid media testing was possible, and coverage of WHO-approved rapid diagnostics (WRD) was sufficient, using line probe assay (LPA) testing since 2003 and HAIN and GeneXpert since 2010 (selected patients). From 2012, 97% of new notifications and 88% of previously treated patients were tested for MDR–TB.
- Dr Leimane described full patient coverage with DST for FLDs and SLDs, using BACTEC/MGIT 960 and LJ medium testing, as well as HAIN GenoType MTBDR sputum-smear testing for high-risk patients.

PV

- The country had links with the Uppsala Monitoring Centre and the State Drug Agency collected recording forms from patient files, which represented a certain level of active monitoring of SAEs (not only life-threatening events). However, no data were available on the extent of doctors' reporting of side-effects and no official reporting system existed for SAEs for all TB drugs (only for Bdq, for which events were reported directly to the manufacturer).
- Plans existed to implement active monitoring, but support was needed to improve these. The existing functional electronic register for PV needed to be built upon and links established with the State Drug Agency to improve the reporting system, along with technical assistance to build capacity for signal detection and data analysis.

Country- or project-level policy related to the introduction of new anti-TB drugs

- No legal framework existed for the introduction of new drugs in Latvia but it was firmly agreed that one was needed. Currently, the Ministry of Health was responsible for decision-making on new drug introduction, procurement and allocation of funding, and the State Drug Agency was the main regulatory body for decisions on permission for compassionate use, registration, importation permission and waivers.
- Key shortfalls were insufficient funding and extensive countrywide resistance.

- International (WHO) policy documents were available and there was a strong desire to put into effect the *Policy implementation package* and develop a protocol for shorter treatment regimens, as well as to introduce the new drugs and provide anti-TB regimens for all patients. However, the country's implementation plan had been stopped at draft stage as the drugs were simply not available, owing to lack of funding.
- The government had allocated funding for new drugs to treat 20 patients in one year, but this was not enough. A stepwise approach to increasing the availability of the drugs was a possibility under the current funding situation, but shortening treatment would be very difficult unless operational research capacity was built to enable shorter regimens, and treatment would fail for many patients.

Discussion

- It was highlighted to Dr Leimane that Latvia could apply to the GDF for Cfz, given the limited number of patients (20), and it was recommended that this be passed on to the relevant actors in the country, as this could help to a certain extent.

Experience-sharing: Kyrgyzstan

Dr Agnes Gebhard, KNCV TB Foundation (international centre of expertise for TB control)

Group V drugs and laboratory capacity

- Planning for the introduction of some new drugs was in the preparation phase, with implementation to begin in 2016. MSF was supporting the introduction of LZD/Bdq/Dlm for a small group of (30–50) patients, and the KNCV TB Foundation was supporting the country's anti-TB efforts through the USAID Challenge TB programme.
- Dr Gebhard outlined current treatment regimens using repurposed Group V drugs for MDR/XDR–TB and three regimens for so-called pre-DR–TB, as well as new (both standard and shorter) regimens planned for 2016.
- She also discussed laboratory capacity to diagnose RR–TB and MDR–TB using rapid diagnostics (HAIN GenoType MTBDR, Xpert MTB/RIB), along with conventional DST in two laboratories, culture testing and capacity to test various SLDs, using HAIN GenoType MTBDR, MIGIT, LJ, etc. Some SLDs were not tested at all, however.

PV

- No official PV system existed in Kyrgyzstan. A drug information centre/PV centre collected and analysed information on ADRs. The centre had two trained members of staff and had published one analytical report, but technical assistance was needed to help build capacity for signal detection and data analysis.
- ADRs were not reported to the PV centre as soon as they occurred, and the concept of PV should also include the monitoring and management of side-effects, ensuring that relevant reporting documentation reached the NTP (and, further up the chain, the Uppsala Monitoring Centre). This was not yet being achieved but was very much intended to be implemented for all MDR–TB patients. Certain drugs would not be available countrywide initially (they would only be provided in certain centres). However, monitoring did not have to be decentralized on a wide scale to be effective.
- Ancillary medicines were a major problem in TB treatment at the ambulatory care level. They were either provided through the United Nations Development Programme (UNDP), through MSF, or purchased using individual TB health facility (hospital) budgets.

- High-quality personnel worked in the NRL, but communication with other levels within the system was poor. The link between the NTP and the PV centre needed to be strengthened, in particular regarding the introduction of the new SLDs.
- A PV module needed to be added to the e-register at the data entry point, and a PV protocol developed. AE and SAE forms needed to be developed, both for reporting and in order to standardize data entry into the e-register. Intensified training on the use of these was essential, supported by all implementing partners.

Country- or project-level policy related to the introduction of new anti-TB drugs

- To be produced, sold and used in Kyrgyzstan, medicines must be registered by the Drug Regulatory Authority/Department of Medicine Supply and Equipment of the Ministry of Health. The registration process took six months to complete, resulting in registration of the drug for five years. WHO prequalified medicines and those authorized by the (strict) Kyrgyz regulatory authorities could be registered within 30–45 working days.
- Access to international (WHO) policy guidance documents was possible, but Russian translation would help a great deal. Country guidelines on so-called pre- and XDR–TB management were to be developed and approved, along with an MSF protocol for the use of the new drugs (awaiting ethics approval). The Drug Regulatory Authority had signed an agreement for fast-track registration with the WHO prequalification programme.
- Waivers were hoped to be possible for importation, allowing faster access to the drugs, but political problems remained to be resolved before this could happen. It was emphasized that this situation was still very unclear and significant need for regulatory scrutiny existed. Updates must therefore be communicated urgently to GDF, before relying on implementation support.

Discussion

- The background of underlying/ongoing political unrest in Kyrgyzstan was discussed, with concerns over the impact this might have on the future use of new anti-TB drugs. Partner collaboration was essential, but the Kyrgyz situation was evidently extremely dynamic. There was therefore an even stronger need to communicate and report back on progress and developments. All parties were hopeful that a joint high-level mission (involving WHO) that had taken place in August 2015 had been useful; communication channels were open, but with a period of elections approaching, the situation was potentially volatile.
- Clarification was sought over whether the primary setting for the introduction of new drugs in Kyrgyzstan was penitentiary or civil. Both sectors had been involved in discussions, but since physical importation of the drugs had not yet been possible, it was too early to determine how they might be used in reality, given the lack of infrastructure and planning.
- It was agreed that regular updates were necessary, in all directions, and it was emphasized that planning was required now – particularly in terms of establishing a basis for importation waivers – in order to avoid becoming "bogged down" or hindered by a rapidly changing political context.
- It was reiterated that, from a technical point of view, drug management was vitally important in the Kyrgyz context as obtaining accurate data on regimens and treatment results was difficult. A database/drug management model was to have been submitted in January 2015 but the GDF had received no further update. However, GF project implementation was intended for Kyrgyzstan and in-country assistance was in progress across three levels: data registry, laboratories (testing) and at pharmaceutical level.

Handover to the NTP was expected in December 2015 and progress would be monitored, in the hope that this would be a sustainable solution, to ready the country for handover of the register from the project hub to the national Ministry of Health. However, miscommunication was a problem, specifically between the project hub and the partners involved. The pharmacy model and future maintenance were also causes for concern, since laboratories had their own interface/database to which the drugs register was not linked, and valid points had been raised about the speed of development of the database/register. However, the recommendation for the moment was to allow the developers to do their job, awaiting evaluation of the system in December, with the opportunity to follow up thereafter. At the moment the need to work together was paramount, and training was required at all levels.

- Clarification was also need regarding funding, since the USAID support was not sufficient, so additional financing would need to be sought, with technical assistance from WHO. The intended plan of action was to create models in three locations and expand from there, with the hope that the country's political situation would not hinder this.

Dr Dara concluded that it had been good to hear the points of view of the attendees, noting that drug interactions in particular were clearly an issue to be considered. He reminded participants to contemplate action points deriving from the workshop, to be discussed the following afternoon.

Day 2. Wednesday 23 September 2015

Session 2 (contd). Objective: to share experiences of countries, rGLC members and partner organizations (technical and donor) that have introduced or supported the introduction of new and/or repurposed drugs into the treatment of DR–TB patients

Experience-sharing: Georgia

Dr Nino Lomtadze, GF TB Programme and National Centre for Tuberculosis and Lung Diseases

Group V drugs and laboratory capacity

- Amx/Clv, clarithromycin (Clr) and Cfz had been used in treatment regimens in the country since 2008; LZD and Ipm/Cln had been available since 2014; and Bdq started to be used in treatment regimens through the Compassionate Use Programme (CUP) in 2011. It had been provided since 2014 under the tripartite MoU and the MSF project that began in 2013, with entry into programmatic use through USAID/Janssen's donation programme in August 2015. Dlm had been available for five patients through the CUP since 2014.
- Programmatic use of available SLDs began in 2008. There was universal access to SLDs, including for so-called pre-XDR and XDR–TB patients, but numbers were declining annually: 501 patients were enrolled in second-line treatment in 2014 and from January to August 2015, the number was 291.
- MDR/XDR treatment regimens have been aligned with WHO TB guidelines – these had been revised and adapted in 2015 and were awaiting ministerial approval. Trials for shortened MDR–TB treatment regimens were ongoing and their introduction was planned. Many patients were eligible for the USAID/Janssen donation programme and the penitentiary sector was already receiving the drugs, with civil sector inclusion planned once the current drugs expired.

- Dr Lomtadze gave a detailed explanation of second-line anti-TB drug use in the country, including regimens, numbers of patients, drug combinations and laboratory network capacity. She explained the recent modification and optimization of the system, with TB diagnosis now integrated in regional public health laboratories. A specimen transportation system was in place, but with uneven performance across the country.
- The diagnostic methods in place were explained in detail and included direct sputum microscopy, Xpert MTB/RIF (in all labs plus the National AIDS Centre), solid and liquid media culture testing, HAIN MTBDR, DST (for both FLDs and SLDs) and rapid DST. Further rollout of Xpert MTB/RIF was planned during 2016 (with additional equipment to be procured for district-level TB units using GF new funding model support).
- The side-effects of LZD were troublesome and ongoing problems with its use were foreseen. This needed to be managed, not only for patient comfort, but also to ensure treatment compliance. It was not enough to focus only on the new drugs (Bdq).

PV

- Active PV had not yet been implemented in Georgia, despite Ministry of Health discussions since March 2014. A dedicated PV contact (ex-Uppsala Monitoring Centre) had been appointed using GF financing, but support for further capacity-building was needed.
- A PV framework for the new drugs was being developed (since May 2015), with technical support provided by Management Sciences for Health (MSH) through the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) programme, and MSF within the endTB project. The necessary documentation was expected to be finalized by the end of October 2015, with staff training to follow. The framework was to include aDSM introduction, with various "packages" for SAE reporting (aiming for routine NTP practice as soon as possible) and special interest AEs, supported by severity-grading standardization training provided by MSF with MSH technical assistance.
- PV issues and drug management needed to be integrated into the new electronic information system.

Country- or project-level policy related to the introduction of new anti-TB drugs

- Lack of experience and capacity for PV at the national drug regulatory authority level and all levels of TB care was a challenge, in particular in outpatient settings, and a major concern was the potential difficulties in enforcing new PV procedures at private institutions (given the size of the private sector in Georgia).
- A minimal legal framework existed for the use of the new drugs, but legal guidelines were needed to support implementation, in particular PV and aDSM developments. Links existed between the SAE reporting function and the regulatory level (through the appointment of a special expert to the SAE review committee), but reporting needed to be encouraged and understood as a shared responsibility between the PV system and the regulatory (ministerial) authorities.
- Documentation required translation, including the international (WHO) policy documents. That said, access to the latter was possible and the guidelines were already reflected in relevant national policies and protocols.
- Implementation of the National TB Strategic Plan (2016–2020) would require drug management capacity to be strengthened, focusing on regimen design for the new drugs and PV more generally. Training on TB management was intended to be cascaded through relevant care levels across the country. Shorter regimens were on the horizon, but

patience was needed to resolve problems and ensure the right conditions for their introduction.
- For the Government to succeed in a stepwise takeover of the essential TB programme, help from external donors would be needed, including for the procurement of FLDs, SLDs and ancillary drugs, along with intensified collaboration with external partners (WHO, USAID, MSH, MSF) regarding the new drugs and implementing the right PV approach.

Discussion

- Dr Lomtadze confirmed that under the MSF funding, a case-by-case (rather than programmatic) approach was being taken to the administration of the new TB drugs in Georgia. Nurses were being trained and paid to visit specific sites to administer TB medication. Ipm outpatient administration was as yet too difficult to organize safely, so these patients were still hospitalized.
- Regarding the specifics of funding additional treatment costs in Georgia, Dr Lomtadze confirmed that the Government covered the costs of additional/ancillary treatment by means of a patient voucher, the value of which had increased almost twofold. A separate voucher existed for so-called pre-XDR and XDR–TB patients. Baseline treatment and follow-up were already funded from the government budget according to the guidance in place.
- Dr. Lomtadze verified that LZD is of greater concern from the AE prospective, since the drug causes difficult-to-tolerate side-effects such as peripheral neuropathy and anaemia that might arise after 2–3 months of treatment and strongly interfere with treatment adherence. In this case, it is reasonable to reduce the LZD dose from 600 mg daily to 300 mg, rather than removing the drug from the regimen, especially taking into consideration the fact that the continuation phase of XDR regimens seems somewhat weak, with Bdq having being removed (although it continues to be circulated). It is therefore essential to keep LZD in the regimen throughout the full treatment. On the other hand, in certain cases MSF was seeking to achieve prolongation of Bdq administration for nine months by the MDR–TB committee, but so far this was not possible. The MDR–TB committee Chair was particularly reluctant, in the absence of supporting documentation to secure against future legal issues. Participants were reminded of the long half-life of Bdq, which meant that side-effects could continue for up to five months after treatment ceased. This – among other ADR concerns – undoubtedly contributed to understandable reluctance from some parties to extend treatment duration. The only workable solution at the moment was to continually collect data from results and build evidence.
- It was expressed that decision-making on these safety issues was not possible without guidance, protection or the necessary documentation, and progress was difficult given that WHO recommended duration limits on Bdq use. Attendees were reminded that data collection was still paramount (where the scope existed to do so, as was the case in Georgia, where Bdq was in programmatic use), as no evidence existed of treatment regimens longer than six months.
- The point was raised that the United States Centers for Disease Control and Prevention (CDC) undertook a different approach to that of WHO, allowing treatment with Bdq and Dlm beyond 24 weeks. It was discussed whether more harm than good was being done by stopping treatment at 24 weeks, leading to increased loss of life by following the recommendations so strictly. The guidelines were in reality providing a framework for data that did not exist. However, a strong feeling existed that most countries in the Region would not go beyond the scope of the recommendations on length of treatment.

Attendees were reminded that clinical responsibility and judgement remained with the treating physicians. It was a so-called chicken and egg situation: if recommendations existed, it was difficult to obtain approval from regulatory authorities to step outside the scope of the recommendations, but simultaneously, many physicians would not act without guidance. The need for access to the drugs was undisputed, but it was reiterated that (patient and drug) safety was paramount. For this reason, the WHO guidance would remain interim, rather than a concrete recommendation, until the necessary picture of the data had been built and analysed.

- Regarding database use in Georgia, Dr Lomtadze confirmed that time was still needed to test, carry out pilot studies and remove bugs before the database (which was being tested) could be relied upon and there was a great deal of scepticism as to how PV-related data could be usefully incorporated. It was yet to be established how the country data could be incorporated into a wider system. MSF had a PV-specific and case-based database but approval needed to be sought before rolling it out in Georgia. Another factor to consider was how patients could access the data, as well as the TB programme.
- It was emphasized that access to treatment safety monitoring tests and instruments was not a problem in Georgia; this was a positive aspect of widespread privatization of TB activities, whereby patients saw a TB specialist each month and had access to the necessary tests (specifically, electrocardiograph (ECG) testing). However, motivating patients to adhere to treatment regimens was problematic, as was coordination between government-funded and private payment mechanisms.

Experience-sharing: Armenia

Dr Armen Hayrapetyan, Director of the National TB Control Centre, Ministry of Health

Group V drugs and laboratory capacity

- Various drugs had been introduced (Cfz in 2006 and LZD and Bdq for compassionate use in 2013), supported by different programmes (MSF, Johnson & Johnson, Ministry of Health), with Dlm due to be introduced for compassionate use under the Otsuka/Ministry of Health CUP in the autumn of 2015 (for which two patients had been approved, awaiting importation). All patients in Armenia had access to treatment if they met the eligibility criteria and approval was granted. Bdq use under the CUP had ended in April 2015, as it was now in programmatic use through MSF funding.
- Dr Hayrapetyan described patient numbers enrolled in various treatment regimens, the TB forms treated (MDR, so-called pre-XDR and XDR) and types of resistance involved.
- In terms of laboratory capacity to diagnose RR–TB and MDR–TB, two molecular methods were available (GeneXpert and polymerase chain reaction (PCR) testing), along with MGIT for FLD and SLD DST, and solid media DST for cycloserine (Cs) and PAS.

PV

- All PV institutions came under the Ministry of Health, with the State Drug Agency as the body responsible for PV. Dr Hayrapetyan described the improvements underway in the SAE reporting processes (developed based on the WHO reporting form) and the side-effects monitoring system intended to be introduced in cooperation with the National Tuberculosis Centre (NTC) for all TB drugs (not only Bdq). Data collection was intended to be reported to the Uppsala Monitoring Centre. AE reporting was carried out according to the rules of the respective manufacturer for each drug.
- The national-level recording and reporting system needed to be standardized, M&E levels increased, and SAE forms adopted across the board to improve reporting quality.

- Training, coaching and support were also needed for TB doctors.

Country- or project-level policy related to the introduction of new anti-TB drugs

- The main NTP decision-making body was the Ministry of Health, with decisions based on WHO recommendations and regulatory oversight by the State Drug Agency. The system was not yet sufficient and needed improvement. Technical assistance was required to help the country handle properly the registration, ordering and importation of the new drugs.
- Access to international (WHO) policy documents was possible but translation into Russian language was needed, as use of the English language was limited in Armenia. The infrastructure for this also needed to be improved in terms of financing the printing and distribution of the guidance.
- Dr Hayrapetyan concluded that political commitment, a legal framework, and adequate financing and resources were needed to address the challenges to sustainable introduction that had been identified. In terms of the legal framework, the application for approval for the much-needed programmatic use of Bdq had been submitted to MSF. Integration of the NTP with primary health care, access to the new drugs and treatment for all patients, and flexibility to enable the required system changes were all necessary elements.

Experience-sharing: Romania

Dr Askar Yedilbayev, rGLC Europe member

Group V drugs and laboratory capacity

- As of the most recent rGLC mission to Romania in March 2015, only Bdq had been introduced for compassionate use for two patients. LZD was found to be used in treatment regimens but its source remained unconfirmed (possibly purchased by patients). Other drugs were not able to be imported owing to the country's regulations but were expected later in 2015. According to the NTP, in September 2015 41 patients had begun treatment with Cfz, Ipm/Cln, LZD and Amx/Clv, without Bdq.
- Since May 2015, Group V drugs were available to Romania through the GF and Norwegian grants. Dr Yedilbayev gave a detailed description of patient enrolment numbers and the plans for expansion of DR–TB treatment in Romania in 2015–2018, with scale-up to programmatic conditions expected for four Group V drugs during that period.
- Dr Yedilbayev described in detail the country's capacity to diagnose RR–TB and MDR–TB, including laboratory numbers and testing capacity (42 level II labs for solid media and DST; two NRLs for LPA MTBDR Plus; and MGIT systems used for culture testing). Plans to expand laboratory capacity during the period 2015–2018 were also outlined.

PV

- A PV system existed in Romania, run by the state and regulated by a national-level drug authority. However, it was for spontaneous reporting only when withdrawing drugs from the regimen (no other side-effects were recorded). An implementation plan was under development by the NTP, with an aDSM plan to be submitted to the rGLC in early 2016, detailing all aspects of Bdq introduction.
- The national PV protocol and guidelines needed to be updated with the latest information on Group V drugs and DR–TB committee members and clinicians needed to be trained in PV matters.

Country- or project-level policy related to the introduction of new anti-TB drugs

- No legal framework existed and this was a complicated and challenging aspect of new drug introduction in Romania. The national strategy for 2015–2020 (approved in March 2015) included some aspects relating to new drug introduction and the NTP was hopeful that all relevant practices could be implemented.
- Bdq had been approved by the national drug authority to be included on the list of medicines for government-funded procurement in September 2015. However, it often took years to update the list so Bdq could now be "stuck in the system". The Ministry of Health and the NTP were also working on introducing Cfz, LZD and Ipm/Cln into the list of government-procured medicines.
- Access to all international (WHO) policy documents was possible but they needed to be translated into Russian and distributed to incorporate updates into the national guidelines.
- Political commitment, sustainability and national financing (once the donor funding ended, as continuity was not assured) would be required in order to introduce new drugs into programmatic use in Romania. Technical support from WHO and partners was also needed, specifically to: scale-up access to Group V drugs; develop the Bdq implementation plan; update guidelines; ensure programme sustainability (including sourcing post-2018 funding); increase programme implementation in outpatient settings, avoiding the pitfalls of the high risk of patients defaulting from treatment regimens in ambulatory care (increasing directly observed treatment (DOT), social support, monitoring and follow-up); and improve the PV system, for which even the basics needed to be put in place.

Discussion

- It was confirmed that technical assistance would be provided to Romania by the rGLC, beginning in October 2015. The hospitalization process would be revised, moving more towards ambulatory care, along with a review of mechanisms and incentives.
- The positive experience and outcomes of the last rGLC mission to Romania in March 2015 was emphasized, including the significant improvements that had been witnessed. Romania was now "catching up" with its European peers in terms of development of systems that would facilitate introduction of the new drugs.
- It was reiterated that a key priority of the rGLC was specific ToRs and that sustainable domestic financing and reforms needed to be carefully considered for the introduction of new drugs. An unprecedented number of missions (and collaborative events) were being undertaken in the Region. In light of the phasing out of GF support in some areas, not only programmatic issues were under consideration, but also financing and health system mechanisms. Collaboration and handover, along with a continued focus on working together, were very important for creating the right conditions to enable policy revision.

Update from MSF on relevant projects

Dr Philipp du Cros, Technical Adviser, MSF United Kingdom

Dr du Cros explained that a minimum set of criteria was required to be in place prior to MSF providing support to a country; six out of eight countries in which MSF provides support to projects had managed to access the new drugs, with varying timescales, legal frameworks and numbers of patients involved. The average timescale for Bdq introduction was 1.5 years and there could be long delays in accessing some drugs, which was known to affect treatment regimens and could lead to resistance. In some cases, countries could access drugs via special

approved importation for pilot projects or approval of the drugs as "humanitarian goods" (for those on the EML), but this was still problematic for Dlm.

He described the process and approach that countries needed to take in order to succeed with Bdq introduction, detailing the key major obstacles before even starting the process and those that needed to be tackled once the process was underway.

Considerations before starting the process of applying for new drugs through MSF included:

- ascertaining what exactly needed to be in place before starting the process (for example, when no functioning PV system existed in many countries, what level of PV actually needed to be in place before starting?);
- establishing appropriate access to treatment services (such as long-term intravenous access for patients);
- understanding the terminology and using it to countries' advantage – for example, "compassionate use" was problematic in many places, especially on a named-patient basis ("life-saving" could work better) and definitions of "operational research" and "programmatic" [use] were complex and needed defining across the board (including within WHO);
- finding the right legal loophole (for example, for approval of pilot programmes) and understanding the difference between strict guidance and guidelines (such as regarding the 24-week treatment limit, rulings on Bdq use for adolescents and children, and the details of PV requirements) – people were suffering and dying while waiting for evidence to be gathered;
- ensuring all drugs were quality-assured (especially Cfz and LZD) and available at the start of treatment regimens to avoid rendering some drugs useless (where treatment had to begin without the new (delayed) drugs) and increasing resistance issues; and
- using a patient-centred approach (studying the patient's treatment history to provide individualized care, rather than taking group evidence as "gospel") – assuming DST (alone) was the best method to determine patient treatment regimens was dangerous (for patients and resistance risk).

Considerations after the process of applying for new drugs through MSF had begun included:

- analysing progress, striving for a continuous cycle of improvement rather than (unrealistically) immediate excellence – starting the process properly for the first patient was the largest hurdle but taking the learning forward could accrue benefits for other patients in future;
- assessing ordering processes – it was better to order individual drugs (such as tablets) than whole treatment courses to avoid stock-outs and wastage through expiry date issues (once patient numbers exceeded 50, stock requirements were easier to predict);
- understanding the pros and cons of compassionate use (of Dlm in particular) – giving options to patients with few treatment options remaining and gaining experience of the drug before introduction into programmatic use, versus limited patient numbers, drug company controls, limited feasibility for scale-up or programmatic use, time limits and legislation/regulation issues; and
- balancing carefully the need for anti-TB drugs with the problems that could arise in moving from drug donation programmes into a more sustainable system – experiences should be shared and outcomes analysed to understand the immediate short-term benefits (such as access to the drugs) versus the longer-term pitfalls, including:
    - sustainability considerations – how to continue when the donation programme ends;

- the scale/extent of the donation (often not meeting needs);
- indication restrictions placed on treatment regimens by the donor;
- recipient selection considerations, involving ethical concerns over differential pricing in different locations;
- delays impacting on access to drugs (whereby negotiations take longer than in commercial transactions);
- cost–effectiveness considerations, bearing in mind additional costs of transportation, storage, etc. to be borne by recipient countries; and
- anticompetitive impacts, whereby domestic manufacturers could not compete with free products.

Dr du Cros also described a short-course treatment trial (not an RCT, but a field-based operational study) under way by MSF in Uzbekistan to amass additional evidence. He detailed the treatment regimens, durations and results, including side-effect monitoring and PV considerations, stating that preliminary outcomes were positive. However, no relapse data were available six months after treatment, and hence caution was needed when looking at early results, especially in relation to the "biased" nature of the patient group enrolled in the study. However, this regimen was unlikely to be suitable for all patients, and data certainly needed clarifying (SAEs were being assessed, along with patients' full case history, in conjunction with clinicians and the established guidance), but it could provide options for certain patients.

In terms of drug prioritization, Dr du Cros stated that new options would emerge as new evidence was gathered and that it was important to stop blindly maintaining the status quo. Instead, new ways had to be considered to streamline the market, predicting future drugs of importance, and move away from multiple choices and treatment regimens, instead procuring drugs on a patient-by-patient basis. Drugs should be considered for removal/de-prioritization if their efficacy could not be established or they caused severe side-effects, and pilot programmes/projects and RCTs should be prioritized over cohort-based RCT research to inform the body of evidence and lead to guidance on (shorter) treatment regimens, not just individual drugs.

He emphasized the importance of thinking beyond donation programmes and to establish or at least understand clearer guidance on the possibilities for "breaking the rules" in order to save lives on a case-by-case basis, rather than adhering strictly to the regulations (which were in many cases irrelevant as they were not based on up-to-date data). If such an approach was not adopted, limited palliative care would become the only available option for many patients. Dr du Cros also reiterated that the emphasis on PV per se was not useful and a more patient-based aDSM approach, along with careful side-effect management, would yield better results in the fight against DR–TB.

Discussion

- Dr du Cros clarified his position on donation programmes, reiterating their usefulness in the short term, particularly for dealing with funding issues and for compassionate use, to "get countries started", but in cases whereby the donation would not last forever (all cases), the long-term perspective needed consideration. It was discussed that, contrary to his view, a great deal of work was done to ensure donation programmes were as effective as possible and a significant body of evidence existed that they were essential, particularly when countries had no other means of introducing new anti-TB drugs.

- Communities needed (expensive) drugs to treat patients and donation programmes provided them, but the message delivered needed to be carefully considered, as the programmes were never "free", as the associated costs (transport, storage, regulation etc.) still needed to be borne by the recipient countries. Sustainability considerations were therefore paramount and countries needed help to maximize resources and to find mechanisms for continued treatment of patients.
- It was expressed that while countries were very grateful for any/all support, and some help was indeed better than no help at all, MSF was raising the standards in countries to such a degree that the programmes were not able to continue at the same level of patient care once support was withdrawn. The focus therefore needed to be on future support and planning, aiming for sustainability, using combinations of approaches rather than one right (or wrong) answer.
- An alternative approach was suggested: namely, anti-TB care also needs to be seen as a social responsibility, rather than relying solely on government or donation funds. In some countries, even with a significant TB burden and thousands of patients, collaborative effort was made by churches, charities and benevolent organizations, working alongside government to ensure an adequate, comprehensive response to patient needs.

Experience-sharing: Russian Federation

Dr Andrei Mariandyshev, Chair of rGLC Europe

Group V drugs and laboratory capacity

- Bdq was registered in the Russian Federation in October 2013, with national recommendations for diagnosis and treatment published in 2014 and approved in 2015. Its use was authorized for MDR/XDR cases (along with other Group V drugs), with plans to change the recommendation to also allow officially for so-called pre-XDR–TB treatment. Regions of the Russian Federation could procure the drugs themselves, with Bdq offered via two drug companies, and to date several hundreds of patients were being treated with Bdq across the country.
- Dlm and Cfz were not registered for use in the Russian Federation. Dlm had begun to be used (in combination with other drugs, since June 2015) in one region, for two patients as part of a CUP. The cases were to be discussed with the TB Consilium and advice was needed on treatment durations, as well as technical assistance with results analysis.
- In terms of laboratory capacity, MGIT testing was available in 85 regions (for SLD DST) and molecular diagnostic methods were expected to be established in all regions by the end of 2015. Plans existed to analyse resistance to injectable drugs, pending ministry regulation. However, not all regions perform DST on SLDs routinely for all MDR–TB cases.
- Dr Mariandyshev described the treatment regimen for XDR–TB patients and explained its complexity in terms of prescribing. Doctors must be encouraged to follow recommendations to prescribe full treatment schedules in order to prevent amplification of resistance. He outlined the results of MDR/XDR–TB treatment with Bdq, resulting in some "failures" and the concerns this raised over the potential development of resistance to Bdq. It was reported that of 54 patients treated with Bdq and on whom outcomes are available, three failed treatment and Bdq resistance was detected by two laboratories in the Russian Federation. For so-called pre-XDR and XDR–TB patients, guidance was needed on how long and which drugs to test and use in treatment. The picture of resistance in the country was unclear and, as such, alarming.

PV

- Monitoring forms existed for spontaneous reporting but doctors in the Russian Federation did not carry out reporting practices and relationships were not good between the PV level and the TB programme. Special analysis and technical assistance were needed to establish what sort of monitoring should be carried out and by whom, incorporating PV into doctors' routine practices.

Country- or project-level policy related to the introduction of new anti-TB drugs

- International (WHO) policy documents were available but were needed in Russian language.
- Further challenges to the introduction of new drugs in the Russian Federation also included the introduction of DOT practices and DST capacity.

Discussion

- Discussion ensued about the technical details surrounding the resistance issues appearing in the Russian Federation, in an attempt to understand the specifics and whether it was laboratory/methodology error, repeated transmission of the disease, or amplified resistance. All patients received free diagnostic tests with GeneXpert; for FLDs this was quick and universal, while for SLDs it depended on the initial FLD DST results. It was confirmed that the laboratories were carrying out testing using the pure Bdq substance (not tablets), and that the patients (both MDR–TB and XDR–TB) concerned were still sputum-smear positive when tested after 12 months.
- The Russian Federation was advised to urgently liaise with the TB Supranational Reference Laboratory (SNRL) in Milan to discuss further action in relation to the stated detected Bdq resistance. The methodology for Bdq DST had not yet been standardized and validated internationally, so if Bdq resistance was suspected, it was vital to coordinate and communicate with the Milan SNRL. Laboratory testing methodologies in laboratories in the Russian Federation need to be checked to ensure compliance with the international recommendations and results must be shared widely, particularly if Bdq mutations were found.
- It was agreed that these "failure" cases were to be reported in full detail (including patient histories) to the rGLC through official reporting channels, for follow-up and joint efforts to resolve the issue.

Experience-sharing: Turkmenistan

Dr Andrei Mariandyshev, Chair of rGLC Europe

Very little information was available about the situation for introducing new anti-TB drugs in Turkmenistan, but the little that was known included the following:

- agreement had been reached to start SLD DST (by LPA and MGIT) at the end of 2015;
- no SLDs were registered for use in Turkmenistan, but were expected to be registered by the end of 2015;
- external help was provided by the International Federation of Red Cross and Red Crescent Societies Red Crescent, with an initial cohort of over 200 patients currently being treated and results expected in 2016; and

- GF support had been secured to procure Bdq for 50 patients during 2016, but this was disputed by the GF as being "too ambitious", as problems remained to be resolved with the regulatory authorities and the infrastructure was not yet suitable.

Discussion

- Dr Mariandyshev expressed the desire that existed in Turkmenistan to implement a new TB treatment model on an ambulatory basis, rather than a purely hospitalized treatment model. He described the basic MDR–TB programme in place, with the model to be built upon for the new drugs, including: availability of GeneXpert in all regions; good sputum-smear sample transportation infrastructure; GF provision of cartridges; availability of MDR–TB drugs; good understanding of patient numbers; new possibilities for prescription; and good treatment management practices.

Experience-sharing: Estonia

Dr Manfred Danilovits, rGLC member, Head of TB Department at Tartu University Hospital and MDR–TB Coordinator for NTP of Estonia

Group V drugs and laboratory capacity

- Dr Danilovits described the picture of DR–TB in Estonia (low incidence but high burden), with a (slow) decline in the number of MDR/XDR–TB cases, but still 20% among new cases and 48% among retreatment cases. However, in comparison with other health care issues in the country (such as HIV and alcohol-related health burden), the TB picture was not entirely negative.
- LZD had been available since 2006, Bdq for compassionate use since December 2013 (six patients) then procured by the Ministry of Health in 2015 (three patients). Dlm was used in treatment for 10 patients, gifted by pharmaceutical company Otsuka as part of a donation programme from February 2015 to June 2015. Dlm was also planned to be procured by the Ministry of Health from 2016.
- Dr Danilovits described the preconditions for the use of new drugs in Estonia, including clinical trials under way for Bdq and Dlm from 2007 to 2012 (ongoing for Dlm Phase III). He also outlined the main regimens used and the differentiation between so-called pre-XDR, XDR and MDR–TB patients, along with the preliminary treatment outcomes, which comprised no serious side-effects related to Bdq or Dlm.
- Estonia had experience with PMDT since 2001 and full laboratory capacity across two laboratories for diagnosis and testing (solid media, BACTEC MGIT, HAIN MTBDR plus and MTBDRsl, plus GeneXpert).

PV

- The NTP had implemented standard AE reporting forms and a routine monitoring system was in place (paper forms with data recoding into a general TB register). However, recording of side-effects was patchy, depending on the willingness of individual doctors. No special warning system was in place for MDR/XDR–TB, but reporting forms were routinely sent to the State Agency of Medicine. For compassionate use of Bdq, the manufacturer's (Johnson & Johnson) SAE forms were used and for Dlm use protocols were introduced by the State Agency of Medicine in cooperation with the pharmaceutical company (Otsuka).

Country- or project-level policy related to the introduction of new anti-TB drugs

- Estonia had benefited from good political (Ministry of Health) and financial (State Agency of Medicines) support to control TB since 1998. An independent decision-making process was in place at the NTP level for compassionate use of the drugs, with a legal framework and regulatory aspects since September 2013. While funding could be an obstacle for future consideration, the decreasing number of MDR–TB cases could positively influence the budget.
- Shorter regimens could also help budgeting issues. The NTP had decided to introduce shorter regimens for the new drugs in an attempt to reduce the side-effects for patients. For MDR–TB this was possible, but a more cautious approach was needed for XDR–TB cases, with long lead times to amass evidence to support continued use of short, individualized treatment regimens.
- International (WHO) policy documents were available, but local guidelines summarizing the content would be needed, as most doctors were not prepared to read lengthy guidance materials.
- Continuous training and motivation of staff, clearly defined reporting criteria, closer patient supervision and follow-up (especially in outpatient contexts) and better links with the State Agency of Medicine were all needed to address PV issues in Estonia. Increasing the responsibility of the TB Consilium could also help.

Experience-sharing: Kazakhstan

Dr Manfred Danilovits, rGLC member

Group V drugs and laboratory capacity

- Dr Danilovits gave an overview of the key figures relating to TB notification, cases registered (MDR: 26.3% new cases and 57.8% retreatment cases) and treatment success rates in Kazakhstan. He explained that there had been many developments over the last year, so it was difficult to assess the environment for the introduction of new drugs. Currently, the country did not have access to new drugs or most of the Group V drugs (Clr, Amx/Clv and moxifloxacin (Mfx) were in use for XDR–TB patients since 2012).
- The country had applied to the GF for support with Bdq introduction, but it was rumoured that the concept note had been rejected, which would affect treatment regimens planned for 200 patients in 2015–2016. The pilot sites selected would receive Bdq under the USAID donation programme instead, but fewer patients could be treated.
- Within the endTB project funded by UNITAID and technically supported by Partners in Health (PIH), up to 600 additional patients could receive Bdq and/or other new drugs (Dlm) in 2016–2017.
- Other Group V drugs were to be procured by the government for programmatic use from December 2015, to ensure complete treatment regimens. This had been the case for 85% of Kazakhstan's procurement the previous year, which meant that should the GF application rejection be confirmed, the funding gap which would need to be managed by the government would only be 15%.
- The drugs for the pilot projects were to enter the country under import waiver as the registration process remained complicated without Phase III clinical trial safety results.
- Dr Danilovits described the extensive countrywide laboratory network and diagnostic capacity, including liquid culture and molecular methods, Xpert MTB/RIF and HAIN LPA for FLDs and SLDs, with expansion planned. All TB patients underwent FLD DST and access to SLD DST had improved considerably in the last two years.

PV

- The existing AE reporting system was limited to spontaneous reporting, with the national drug authority collecting all AE forms, including those relating to TB. Currently, side-effects were only recorded in patients' files, with no information reporting or sharing, but extensive adaptation of the system was planned, focusing more on PMDT.
- For the endTB project, a dedicated PV services unit was planned to be organized in Geneva (run by MSF), but no specific national plans were in place to improve the PV system. However, closer scrutiny of drug safety had been highlighted in planning, and data collection on SAEs under the UNITAID project would be reported to Geneva and shared with the NTP.
- PV databases, recording of results and other clinical/laboratory information (not currently a routine part of PMDT) and treatment and follow-up recording were in the process of being strengthened and harmonized with technical assistance from the KNCV TB Foundation and PIH. Long-term support and technical assistance would be required to improve PV practices in the field, including information and training for doctors and health personnel, increased human and financial capacity, and additional Bdq-specific monitoring and supervision measures.

Country- or project-level policy related to the introduction of new anti-TB drugs

- Strong political support existed in Kazakhstan for TB control in general and for introducing new tools for PMDT, along with multiple partners supporting the development of a framework for introducing new technologies and a government keen to fund such work.
- The status of the national implementation plan for Bdq was not clearly defined, but a long-term training plan and treatment guidelines were being developed, with support from PIH. A technical working group was required to assist with implementation of new drug policy and tackle differences in approach by the NTP and the Ministry of Health.
- Access to international (WHO) policy guidance was possible but lack of English language in Kazakhstan (including among doctors) meant that translation into Russian was essential. Health personnel awareness of new guidelines also needed to be raised.

Discussion

- It was emphasized that importation of drugs was highly problematic, with delays of up to six months, which affected treatment and had knock-on effects in terms of shelf life (particularly Bdq). Where quality concerns were raised, it was essential that these were dealt with in full, given the high patient numbers in Kazakhstan (over 6000 MDR–TB cases). How this would be affected by Kazakhstan recently joining the Eurasian Customs Union with Belarus and the Russian Federation, among others, needed to be evaluated.
- It was agreed that documentation support was clearly needed for waivers; the country was working with the GF to improve ordering and shipment processes. In terms of the concept note rejection, the official word from the GF was that issues remained to be resolved, but no official decision had yet been made. Resolution of the matter was expected by December 2015, and an assessment mission was planned to the country in November 2015 so the situation on the ground would be assessed soon.

Experience-sharing: Pakistan (the extra-regional perspective)

Dr Aamir Khan, Executive Director, Interactive Research & Development (IRD), Project Lead for endTB project

Group V drugs and laboratory capacity

- Dr Khan described the situation in Pakistan, highlighting that no method existed to introduce new TB drugs apart from through the projects being conducted at the Indus Hospital, Karachi. Bdq had been ordered from the GDF and the country was ready with the necessary systems and cohort to start treatment in the final quarter of 2015. Dlm was also planned to be introduced but the timeline was as yet unclear. Cfz, LZD, Amx/Clv and Clr were already in use, some under compassionate use programmes (Cfz) and some introduced through the NTP (LZD), although local procurement issues had arisen with LZD. He described the patient enrolment numbers for the Indus-IRD TB programme, detailing drug combinations and resistance differentiated by site.
- Pakistan had a significant laboratory structure and was working towards external quality assurance. GeneXpert, liquid and solid culture testing, and FLD and SLD MGIT testing were available for RR/MDR–TB diagnosis, as well as extensive laboratory capacity for SLD DST.

PV

- MSF was to host a PV unit for endTB project sites, with up-line PV reporting and an early monitoring and reporting system that was designed to be "more than just a medical record". Trained on-site PV personnel would carry out SAE reporting through individual reporting forms, with periodic up-line transmission of non-serious AEs. All patient and PV data were to be collected on EMR, combining several open-source platforms for a comprehensive, combined approach.
- A new SMS-based AE alert system was also ready to be activated, based on open-source software that IRD was willing to share. The system used mobile phone-based reporting "forms" for alert and tracking functions, as well as treatment monitoring, with multiple points of capture (including patient, treatment support personnel and physician). Designation of severity and monitoring of response times were also incorporated. An endTB observational study would collect and analyse data on AEs and outcomes.
- The national PV committee comprised multiple national and provincial actors, external advisers, clinical experts and endTB managers working to monitor the roll-out of new drugs, oversee all immediate reporting of SAEs and quarterly updates on (non-serious) AEs, and review individual difficult cases for a patient-centred response.

Country- or project-level policy related to the introduction of new anti-TB drugs

- Pakistan had access to all international (WHO) policy documents, and approval for introduction of the new TB drugs had been received from the Technical Working Group on Tuberculosis, with introduction to be strictly based on WHO guidance. The drugs were to be procured by obtaining importation and registration waivers, with Bdq accessed through the USAID/Janssen donation programme.
- Training on the guidelines and forms to be used was being conducted in preparation and would continue, and with NTP support, the IRD would focus on capacity-building and training of trainers (to cascade training) in both the public and private sectors.
- Key needs for the way forward included: improving access to drugs; moving manufacturers' focus away from single drugs to producing effective treatment regimens; implementing more clinical trials to treat DR–TB; and ensuring supply matches demand, to avoid unforeseen shortages. In addition, advocacy and technical support were both needed to help the country follow WHO recommendations for introducing the new drugs, and the existing systems and models needed to be built upon and public–private sector collaboration strengthened to improve treatment outcomes.

Discussion

- Owing to devolution, roles were not clear, but it was clarified that the PV unit that existed at national level was not yet fully functioning. However, the NTP had requested support in the form of a project-specific committee to help with the introduction of Bdq and had established a project-level PV committee with multiple agency representation.
- It was explained that the apparent difference in MSF and IRD approaches (despite belonging to the same project) was due to the various deliverables that the project required. National-level and project-level requirements were different and in fact the data recorded in each setting would not be useful to the other; this was not a contradiction in approaches, but rather a differentiation.
- Dr Khan clarified that a global shared database was used to report treatment results. It was also used by Bangladesh and Indonesia within the project, along with MSF. Each country had its own database with the same structure and a shared basis.

Laboratory-related rGLC challenges in the WHO European Region

Dr Sabine Rüsch-Gerdes, member of rGLC Europe

Dr Rüsch-Gerdes presented the key needs for using Group V drugs, making the following points.

- Availability of the drugs was necessary. If drugs were not used in treatment regimens, there was no need to carry out DST on them. It was more useful to save the money and the human resources allocation for use elsewhere.
- A high-quality laboratory system was required, with high safety standards and appropriate infrastructure. Adequate policy reform at national level must be implemented to strengthen TB diagnostics. This included a quality-control system for all methods used and drugs handled. Brussels was asking SNRLs to test and share their results, and such results were more likely to be accepted by clinicians. Better communication and improved processes would lead to the development of resistance strains being stopped.
- Well-trained staff were also needed to correctly identify resistance using modern diagnostic techniques. Having high numbers of consultants was not an effective approach, either; rather, a good laboratory infrastructure, training on equipment and results validation, and equipment maintenance from specialists would all contribute to early, rapid and accurate detection of DR–TB.

Dr Rüsch-Gerdes explained that progress was being made, with external reviews and assessment missions gradually being accepted. Review results were showing that countries were beginning to (or needed to begin to): establish laboratory infrastructure with appropriate biosafety measures; validate and maintain equipment; manage laboratory commodities and supplies; implement a data management system; coordinate adequate strategies, technical assistance and funding mechanisms; and integrate diagnostic algorithms. These were examples of preconditions for good laboratory results, which would progressively lead to: increased acceptance of the requirements, improvements in laboratory quality, more rapid detection of DR–TB strains, more reliable data and, ultimately, better treatment outcomes.

Key challenges included:

- implementation of DST for all SLDs;
- quality control concerns over: purity of substances; and SLD DST, including Group V drugs (cooperation with the country's SNRL was necessary);

- collaborative working with international organizations needed improvement;
- ordering issues, whereby some drugs were very expensive and problems were encountered with customs/importation regulations – a suggestion to overcome delays was to discuss openly with the factory or company concerned, asking for a free sample (direct order) of a small quantity for laboratory testing, not research or treatment (and be prepared to store correctly and observe expiry/disposal requirements to avoid waste);
- promoting WHO strategies and adherence to guidelines through high-quality, evidence-based education – for this, technical assistance needed to be provided to the national reference centres (NRCs) on how to train staff and cascade learning and quality improvements throughout the system (and guidelines should be made more concise, with a standardized algorithm and available in different languages); and
- using initiative and thinking outside of the guidelines as well, with different approaches for different substances, depending on the problem encountered and the country context.

Dr Rüsch-Gerdes went on to explain how these issues could be addressed, including through: supervision (by WHO), with assessment missions to identify and address gaps; increased involvement and cooperation of national and international partner organizations, using a common (scientific) language to avoid subjective interpretation, and continuity of personnel to form strong working relationships; efforts to convince politicians of the importance of laboratories and their results, increasing their willingness to fund laboratory activities accordingly; and use of rapid, accurate diagnostic techniques and transmission of the results to clinicians (with external quality assurance by the rGLC and SNRLs).

It was also necessary in the European context to be sure of concentrations for Group V drugs (with a Cfz study soon to be finalized and published). A "gold standard" of adequate methods should be the goal, reaching agreement on critical concentrations through comparisons of strains. Checking for mutations was also essential.

Discussion

- Dr Rüsch-Gerdes clarified that should NRLs need guidance on reference standards and locations for drug procurement, they should contact their SNRL, which would be willing to help with general or individual problems.
- It was expressed that in the past, the general trend had been for diagnosis to precede treatment (for example, in 2011–2012), whereas now treatment was moving ahead of diagnostic methods – attention was focused on drugs and regimens and it seemed that the sector was forgetting that effective management (PMDT) would always depend largely on diagnosis and this was especially true for the Region, with its high MDR–TB rates.
- The quality of DST was known to be variable in many of the high-burden countries of the Region. One suggestion was that training and support to NRC personnel should be increased to enable them to understand the system in full and communicate important points. It was agreed that intensified intercountry work was needed to strengthen laboratory capacity (one laboratory expert was already on board) and share experiences to enable improvements.
- Technical discussion ensued regarding DST of specific SLDs and results found. The general conclusion was that reliable testing options were available (albeit expensive), laboratory quality was high and external quality assurance was in place for SLD testing. Review of molecular LPA testing for FLDs and SLDs would be ongoing in 2016 (this is currently not recommended by WHO but could be used clinically, with caution, as part of a ruling test for quinolone resistance).

- A practical suggestion to be passed on to all countries was that the strains should be stored and archived (which was possible with just a small freezer), using them to "work backwards", for future learning. This already formed part of the guidance so countries needed encouragement to begin, backed by governments and potentially starting with RCT trials, scaling-up in time to programmatic, routine practices. Discussion would be required among the workshop participants as to where and when routine samples would be needed and where capacity could be built.
- The need was expressed to try to understand resistance amplification. Data analysis was necessary to establish whether it was brought about by reinfection from hospitalization or a new strain of resistance, and the distinction needed to become part of routine practice (supported by laboratory work, supranational centres and partners). Such analysis could be used as proof to show clinicians that sometimes the problem is re-transmission and changes could be implemented in the system to carry forward the knowledge. MSF was also very interested in testing and transmission results.
- For effective treatment decisions, specimens must be transported and analysed quickly, without months of waiting (innovation was needed to this effect, backed by governments). GeneXpert and other diagnostic techniques were useful but results could be discouraging: the machines produced information but did not change the system or treat patients – the information should be used to effect system-level performance changes and improvements.
- It was difficult to obtain political commitment for the evolution of testing, but without SLD testing results, MDR–TB prognosis could not be affected. Genotyping must become a standard (albeit expensive) goal. The question was raised as to how gene sequencing could be introduced, especially in the wider (global) WHO context, whereby policy was not tailored exclusively to the European Region; elsewhere, the focus was different and diagnosis was far from being ahead of treatment, with policy changes taking a long time to implement.
- Increased biosafety training was cited as a key laboratory-based need. Dr Rüsch-Gerdes reiterated that training could be cascaded so was only needed once and therefore did not need to be cost–prohibitive. It was discussed that countries could also contribute to increased efficiency, and that regional-level collaboration could be very useful.

Introduction and access to new drugs for DR–TB treatment under the GF funding model

Dr Martin van den Boom, on behalf of the GF

GF support for DR–TB over the period 2012–2014 had increased threefold, contributing directly to the scale-up of MDR–TB response in the Region and to the introduction and scale-up of Xpert MTB/RIF diagnostic testing. The rGLC was supported with funding to provide technical support to the respective countries. More focus was being placed on MDR–TB as a priority, even with the shifting of funding, and constant support could still be provided.

Under the GF's new funding model, diagnosis and treatment targets had been revised, the scale-up of diagnostic services would be aligned with treatment and the emphasis on TB and MDR–TB balanced; treatment would move away from the inpatient sector into ambulatory care; increased domestic and other sustainable funding sources would be leveraged; and alongside the introduction of the new drugs, support would be provided for active PV and capacity-building.

Regarding the introduction of the new drugs and shorter DR–TB treatment regimens, some countries were already accessing GF financing; funding requests could include establishing/strengthening active PV, patient support and companion drugs, or technical assistance with capacity-building (for example). The GF was collaborating with USAID (among other partners) to ensure: (a) no overlap (countries receiving Bdq through the donation programme could re-programme funds to support PMDT activities); and (b) alignment with the End TB Strategy and the global TB plan.

Through the extension of the MoU until the end of 2016, the new WHO–GF GLC agreement signified heightened country ownership, with more emphasis on countries supporting the implementation of GLC arrangements. Monitoring and evaluation missions were required (with new parameters for ToRs), revised reporting requirements would come into effect and reports needed to be finalized more quickly than previously to ensure additional quality assurance steps were covered in time. The MoU provided for technical support for PMDT (with consultations to be carried out to shape technical support options), but also called for increased collaboration, evaluation and analysis of what is and is not being implemented at country level, and why, along with provision of performance-based and quality-assured services.

Discussion

- The rGLC members expressed their need to understand the full impact of the changes the amended MoU introduced at country level, particularly regarding GF eligibility criteria (whereby other funding sources would be required). The new terms meant that mission reports were now to be reviewed, with funding allocated in two tranches (the second tranche dependent on submission to the GF of a peer-reviewed rGLC monitoring report but – crucially – to be paid anyway after 30 days of inaction by the GF following submission of the report). This may not be of particular concern to the European Region as the countries' peer-review mechanisms and reporting were already of high quality, so this could be viewed as simple information-sharing. For other WHO regions, however, stability of funding was now far from guaranteed.
- The MoU was linked directly to USAID support, but this did not in reality affect many of the European Region Member States (with high MDR–TB burdens). Countries in other regions would be affected, losing funding, along with GF grants with MDR components.
- Funding would continue to be available for in-country MDR–TB-related activities through partners such as Challenge TB, requiring collaborative working by countries "on the margin" of being affected by the MoU, in order to improve funding mechanisms and increase access to funding. More advanced planning, and budget analysis and allocation were going to be required. It was important to remember that additional technical assistance could still be requested from the rGLC, albeit through different (countries' own) funding mechanisms.
- As this was an amended, restated MoU, many questions would remain unanswered for an interim transition period. However, missions did not need to be cancelled, and some flexibility existed in terms of dates when funding had been agreed; changes would be in effect from the date on which the MoU was signed (3 June 2015) and technical assistance would be "tailored appropriately" to country needs where fewer than 10 estimated MDR–TB cases exist.
- Discussion of different funding mechanisms and possibilities was needed, along with analysis and sharing of various country-specific experiences, and collaboration with partners was even more important than ever.

Session 3. Objective: to plan the next steps for the introduction of new and repurposed drugs for the treatment of DR–TB patients in the countries of the WHO European Region

Dr Fraser Wares, Dr Martin van den Boom

Participants were thanked for their contributions to the workshop and reminded that this was the first of a series of six regional workshops.

The need for follow-up was clear and at regional level, compiling a list of next steps included identifying gaps and assistance needs (and then finding methods to ensure those gaps were filled and needs met). The methodology for the final session of the workshop was to devise a list of next steps from the point of view of the participants. Broadly, these next steps could be collated under five headings.

Laboratory considerations

- Technical assistance was required to strengthen laboratory capacity to undertake DST for key SLDs, including the new drugs and certain Group V drugs, as well as to develop/update existing diagnostic algorithms to include additional treatment options with those drugs.
- If capacity to undertake DST for new drugs was not available in-country, guidance was needed on storage of samples from all patients treated with Bdq and Dlm. Specimens and frequency of specimen collection for storage needed to be determined (but certainly at the start of treatment and upon failure, where relevant).
- International agencies needed to provide support for samples to be exported from the respective country to an SNRL for specialized testing.
- Training of the heads of the respective NRLs needs to be strengthened.
- The Laboratory Network for Europe Initiative needs to be reinvigorated.

Access to drugs

- When ordering Bdq from the GDF, countries should plan for a six-month delivery time. They should also consider ordering partial tranches of Bdq to be delivered, rather than planning to receive all the drugs in a single delivery.
- If countries were accessing Bdq through the USAID “donation programme”, they needed to ensure the availability of the required funds for distribution and storage of the drug, procurement of the other required (companion) SLDs, and all other activities relevant to introducing the drug.
- Advocacy activities were needed to highlight the need for lower dosages of certain drugs (such as LZD) and paediatric formulations of all SLDs to be made available. Bdq should also be made available in strips of tablets, rather than jars.
- Technical assistance was needed to improve projection of SLD needs in many countries, with deaths and local failure rates taken into consideration. It should be noted that tools to assist with this task were available and needed to be utilized better to leverage savings/efficiency gains. Baseline work should be carried out in countries and updated regularly, reflected in drug supplies.

Recording and reporting

- Guidance and technical assistance were required to map where patients on new drugs are situated within a country and to ensure appropriate disaggregated data collection of interim and final treatment outcomes from those MDR–TB patients treated either with new drugs and/or shorter regimens. Recording and reporting systems might need revision to allow for such disaggregated data collection of treatment outcomes. No matter the treatment duration or regimen details, all outcomes should be separated as well as cohorts analysed, to guide proper reporting, data input and analysis.
- Special attention was needed to monitor the distribution and costing of Bdq in the Russian Federation and those countries that had joined the recently established Eurasian Customs Union. Pricing might become fixed, with negative consequences for countries that did not have access to GF funds.
- Mechanisms needed to be established to rapidly and widely share results from ongoing pilot or planned projects (such as interim outcomes from shorter regimens and/or under the endTB project). Databases could be used to quickly pull together evidence.

Programmatic (PMDT) considerations

- Guidance and possible technical assistance were required to:
  - develop protocol(s) for introducing the new drugs as required, with specific help for some countries on the finer points of exactly how to do so;
  - strengthen ambulatory care mechanisms, including basic DOT systems to deliver twice-daily doses of Dlm and injectables such as Ipm/Cln;
  - develop protocols for implementing the required aDSM, including in the move towards increased outpatient care, and involving the required level of social support; and
  - develop guidelines for infection control and palliative care, followed by implementation, supervision and monitoring.
- In-country treatment consiliums needed training on the introduction of the new and/or repurposed drugs. The potential role of the rGLC in this area needed to be explored.
- A roster of clinical experts needed to be created, ready to answer questions on the use of the new drugs from countries about to embark on implementation. The possibility of expanding the current role of the European Respiratory Society (ERS)/WHO TB Consilium to include this should be explored. Expert opinions should be harmonized where possible to avoid sending mixed messages to countries.
- A body of evidence needs to be built to demonstrate the effectiveness of certain Group V drugs, such as Amx/Clv and Clr.

Legislation

- All technical partners needed to assist the respective countries with issues relating to registration and importation of the new and/or repurposed drugs, including providing assistance on obtaining waivers and/or establishing compassionate use programmes.

A crucial and overarching recommendation from the participants was the need for consistent messages and/or guidance from the various bodies and experts who visit the respective countries.

Regional technical advisory groups (such as STAG–TB) would be a good source of advice on many of these matters.

Participants were thanked from a regional perspective for their input and encouraged to send any further feedback they might think of. The key learning points for consideration would be taken forward in the Technical Advisory Group meeting scheduled for 9–10 November 2015. From the attendees' point of view, thanks were extended to WHO for the invite and it was expressed that it was interesting and a privilege to attend such an event, with plenty of work to be done going forward.

Annex 1

MEETING AGENDA

Tuesday 22 September 2015

Welcome and meeting objectives

Session 1. Objective: to provide updates on current WHO global and regional policies, guidance and plans

- Update on new regional TB Action Plan 2016–2020
- How to introduce the new and repurposed drugs into programmatic use for the treatment of DR–TB patients
- Update on current WHO policy recommendations on the use of new drugs (interim guidance on Bdq and Dlm), Group V drugs and repurposed drugs in the treatment of DR–TB patients
- Update on current overarching WHO programmatic management of DR–TB (PMDT) policies and guidance, focus on overarching PMDT, including recommendations on the use of Group V drugs and repurposed drugs in the treatment of DR–TB patients and ethics and palliative care
- Safety monitoring of drugs used to treat DR–TB patients
- Update from the European rGLC Secretariat
- Update from the Global Drug Facility (GDF) on Group V product availability, policy to access these drugs and updated prices
- Perspectives on the introduction and access to new drugs for DR–TB treatment, and an update on the Bdq donation programme and its coordination with other partners and programmes

Session 2. Objective: to share experiences of countries, rGLC members and partner organizations (technical and donor) that have introduced or supported the introduction of new and/or repurposed drugs into the treatment of DR–TB patients

- Republic of Moldova
- Tajikistan
- Azerbaijan
- Latvia
- Kyrgyzstan

Wednesday 23 September 2015

Session 2 (contd)

- Georgia
- Armenia
- Romania
- Update from MSF on relevant projects
- Russian Federation
- Turkmenistan
- Estonia

- Kazakhstan
- Pakistan (the extra-regional perspective)
- Laboratory-related rGLC challenges in the WHO European Region
- Introduction and access to new drugs for DR–TB treatment under the GF funding model

Session 3. Objective: to plan the next steps for the introduction of new drugs and repurposed drugs for the treatment of DR–TB patients in the countries of the WHO European Region

Annex 2

SCOPE AND PURPOSE

Background

New drugs approved by regulatory authorities, notably bedaquiline and delamanid, as well as repurposed drugs classified as Group V in the WHO *Companion handbook to the 2011 guidelines for programmatic management of drug-resistant tuberculosis* (PMDT) are increasingly being introduced in the treatment regimens for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB patients. WHO/Global TB Programme (GTB) issued interim policy guidance on the use of bedaquiline in the treatment of MDR–TB in mid-2013 and on the use of delamanid in October 2014. However limited data, particularly on safety, are currently available on these new drugs, and also on the safety and efficacy of the repurposed drugs listed under Group V. It is therefore imperative that adequate provisions for safe, rational and effective use of these drugs be put in place, specifically ensuring appropriate selection of eligible patients, informed consent, design of effective regimens, and close patient monitoring and evaluation. Both drug stock-outs and overstocking should be avoided and orders aligned to treatment regimens recommended by WHO. Furthermore, WHO/GTB is recommending that countries introducing new and repurposed Group V drugs establish active pharmacovigilance to rapidly detect potential drug adverse events.

Given the essential role of the regional Green Light Committees (rGLCs) as the primary point of contact for country guidance and advice on PMDT, it is very important that rGLC members and PMDT consultants are fully au fait with current WHO policy recommendations on the use of new drugs, as well as those in Group V. A series of workshops are planned by WHO for rGLC members and their respective rGLC Secretariat focal points, while encouraging countries and partners to make use of the rGLC mechanism to ensure that treatment principles and drug orders are aligned with WHO guidelines.

Objectives

Objectives of the joint WHO headquarters/WHO Regional Office for Europe experience-sharing workshop on the introduction of new drugs for DR–TB treatment in the WHO European Region are to:

- provide an update on current WHO policy recommendations on the use of new drugs, as well as those in Group V, in the treatment of DR−TB patients, and how to introduce the drugs into programmatic use;
- share experiences of countries and partner organizations which have introduced new and/or repurposed drugs into the treatment of DR−TB countries; and
- plan the next steps for the introduction of new drugs and repurposed drugs for the treatment of DR−TB patients in the countries of the WHO European Region.

Annex 3

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Annex 3

TEMPLATE FOR EXPERIENCE-SHARING PRESENTATIONS

Key aspects on group V drugs

- Which group V drugs (Cfz, Lzd, Bdq, Dlm, etc.) introduced?
- As of when?
- How many patients enrolled *(per year and drug, please specify the full regimen, treatment duration and country or project (i.e. which scale, full-scale or pilot?).*
- How many patients enrolled *(per year and drug, please specify the full regimen, treatment duration and country or project (i.e. which scale, full-scale or pilot?).*

Key aspects of laboratory capacity

- Details available regarding laboratory capacity to diagnose RR− or MDR−TB *(i.e. drugs tested, which method used, etc.).*
- Details available regarding laboratory capacity SL DST *(i.e. which drugs, by which method, etc.).*

Pharmacovigilance (PV)

- Does the country or project have or follow a clearly defined PV framework?
- If not, what are the plans to introduce – at a minimum – active TB drug safety management and monitoring?
- If so, what areas need to be particularly addressed or improved?

Country- or project-level new drug-related policy

- Does a legal framework (under different terms and conditions, including for compassionate use or pilot projects, importation waivers, etc.) for introducing new TB drugs exist?
- Is it sufficient? If not, which are the shortfalls?
- Does the country have access to international (WHO) policy documents?
- If so, what are the key challenges in applying them?

Key needs and way forward

- What is needed to efficiently address identified challenges for sustainable introduction?