Report of the Ninth Meeting of the Regional Advisory Committee on MDR-TB (rGLC SEAR)

Kathmandu, Nepal, 17–19 October 2016

World Health Organization
Regional Office for South-East Asia

SEA-TB-369
Distribution: General

Report of the Ninth Meeting of the Regional Advisory Committee on MDR-TB (rGLC SEAR)

Kathmandu, Nepal, 17–19 October 2016

World Health Organization
Regional Office for South-East Asia

Printed in India

Contents

Acronyms

aDSM	active drug safety monitoring and management
Bdq	bedaquiline
CDC	Centers for Disease Control and Prevention, Atlanta
Dlm	delamanid
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility test
FQ	fluoroquinolone
EQA	external quality assessment
GF	the Global Fund
GDF	Global Drug Facility
GDI	Global Drug-Resistant Tuberculosis Initiative
KNCV	Royal Dutch Tuberculosis Association
MDR-TB	multidrug-resistant tuberculosis
MoH	Ministry of Health
MoU	memorandum of understanding
NSP	National Strategic Plan
NTP	National Tuberculosis Control Programme
NTRL	national tuberculosis reference laboratory (ies)
PMDT	programmatic management of drug-resistant tuberculosis
PPM	public-private mix
PSM	procurement and supply chain management
PV	pharmacovigilance
rGLC	Regional Green Light Committee

RR TB	rifampicin-resistant tuberculosis
R&R	recording & reporting
SAARC	South Asian Association for Regional Cooperation
SEAR	South-East Asia Region
SLD	second-line drugs
SLI	second-line injectable
SNRL	supranational reference laboratory (ies)
STR	shorter treatment regimen (for RR/MDR-TB)
TB	tuberculosis
The Union	The International Union against Tuberculosis and Lung Disease
TWG	technical working group
UHC	universal health coverage
UN	United Nations
XDR-TB	extensively drug-resistant tuberculosis

1. Background

As per the 2016 Global TB report,[1] the estimated incidence of multidrug resistant and rifampicin resistant (MDR/RR-TB) in the WHO South-East Asia Region (SEAR) was 200 000 cases in 2015. The MDR/RR-TB cases estimated among notified pulmonary cases in the same year were 110 000 out of which 35 953 cases were diagnosed using laboratory confirmation. Out of the laboratory confirmed cases, 32 648 were started on treatment. Of all the MDR/RR-TB cases initiated on treatment in 2013, only 49% were successfully treated in SEAR. Extensively drug-resistant TB had been reported by six countries in SEAR by 2015.

At the Sixty-second World Health Assembly in May 2009, Resolution WHA62.15 was adopted and Member States urged to develop and implement long-term plans for TB, including MDR-TB and extensively drug-resistant tuberculosis prevention and control. One of the actions taken to implement this resolution was to revise the Green Light Committee Initiative by decentralizing its services to strengthen support to countries to access high-quality second-line anti-TB drugs, and to enable them to provide treatment for people with MDR-TB in line with WHO guidelines. In response to the need for scaling up the programmatic management of drug-resistant tuberculosis (PMDT) in the WHO South-East Asia Region, a Regional Advisory Committee on MDR-TB, also known as the regional Green Light Committee (rGLC), was established in 2012. The rGLC functions as Advisory Committee to the WHO Regional Office for South-East Asia, WHO Member States in the South-East Asia Region (SEAR) as well as donors and partners.

The first and second meetings of the Committee were held in May 2012 and December 2012 at the WHO Regional Office for South-East Asia, New Delhi, India; the third and fourth meetings were held in April 2013 and November 2013 in Thimphu, Bhutan, and in Jakarta, Indonesia, respectively; the fifth, sixth and seventh meetings were held in May 2014,

[1] *Global tuberculosis report 2016, World Health Organization, Geneva 2016.*

February 2015 and August 2016 in Mumbai, India; Dhaka, Bangladesh; and Mandalay, Myanmar, respectively. The eighth meeting of the rGLC was held in Bangkok, Thailand, from 8 to 10 March 2016. During these meetings, the Committee reviewed and endorsed the country mission reports on PMDT and extensively discussed issues related to the scale-up and implementation of PMDT in countries of the Region.

This report pertains to the proceedings of the ninth meeting of the rGLC held in Kathmandu, Nepal, from 17 to 19 October 2016. The meeting was combined with a workshop for high-burden countries on adoption of 2016 WHO guidelines on DR-TB diagnostics and treatment of DR-TB.

2. Inaugural session

The meeting was inaugurated by Chief Guest Mr Bhogendra Dotel, Chief Policy Planning and International Cooperative MoH, Nepal, along with Dr Nihal Singh, Acting WR WCO Nepal, Dr Bikash Lamichane, Director NTC, MoH, Nepal, Dr Md Khurshid Alam Hyder, Regional Adviser TB, WHO/SEARO and Dr Sarabjit Chadha, Deputy Regional Director, Union and Chair SEAR MDR-TB Advisory Committee. The Chief Guest in his inaugural speech gave an overview of the TB control programme in Nepal. He stated that there are nearly 4000 treatment centres and 581 microscopy centres as of now. Annual new case load in Nepal is estimated around 44 000 TB cases whereas close to 35 000 cases are being currently notified. He emphasized the need to reach vulnerable populations and children. MDR-TB needs to be addressed. The National Strategic Plan for TB control in Nepal is based on principles of accountability, availability and multisectoral approach. In the coming years, the priorities of the national programme include conducting prevalence surveys to estimate disease load and drug-resistance surveys among TB patients.

The acting WR welcomed the Chief Guest and participants to the workshop. He said that the Region bears half the global burden of TB and the highest burden of MDR-TB as well. The year 2016 marks the beginning of End TB Strategy with a bold vision of ending the TB epidemic in the Region by 2030 in alignment with the UN Sustainable Development Goals. There is a need for faster implementation of strategies, adoption of new

tools and technologies and providing quality care to all those who need effective TB control. He stressed the need for the adoption of the new WHO guidelines on MDR-TB.

The Chair of the rGLC reiterated the fact that the Region bears the highest burden of MDR-TB. He stated that the rGLC is a group of experts providing technical assistance for strengthening MDR-TB response in the Region. Several challenges exist in the Region, most of them because of the suboptimal health systems. The rGLC helps find solutions to these problems and designs future strategies to effectively combat MDR-TB.

RA-TB provided an overview of the current rGLC structure and organization of the current meeting. He then briefed participants on the objectives of the meeting.

3. Objectives

- undertake technical discussions focusing on the uptake and modalities of implementation of the new WHO guidelines on MDR-TB (May 2016) (Day 1);
- prepare operational plan for introduction of shorter regimen (Day 2);
- review progress in the implementation of the recommendations of the eighth meeting; and
- discuss strengthening of rGLC mechanism to improve technical assistance on MDR-TB in the Region (Day 3).

4. Technical sessions

Day 1

Global and Regional burden of TB

Globally in 2015, there were an estimated 10.4 million incident cases of TB. Six countries accounted for 60% of the new cases: China, India, Indonesia, Nigeria, Pakistan and South Africa. The global estimate for TB

burden has seen considerable upward revision compared to earlier years due to revision of India estimates. In 2015, the gap between notifications of new cases and the estimated number of incidents was 4.3 million (missing cases), reflecting a mixture of undetected cases and under-reporting of detected TB cases.

Inauguration of ninth rGLC meeting by Chief Guest Mr Bhogendra Dotel.

In the South-East Asia Region in 2015, there were an estimated 4.74 million incidences of TB and about 784 000 people died due to TB. Total number of new cases notified to national TB programmes of the SEAR were around 2.65 million cases in 2015. SEAR accounts for 45.6% of the global burden in terms of TB incidence. Six SEAR Member States are in the list of 30 high TB burden countries. These countries are Bangladesh, Democratic People's Republic of Korea, India, Indonesia, Myanmar and Thailand.

In 2015, 6.4 million people with TB were notified by NTPs globally. Total TB cases notified in SEAR were 2.7 million.

Globally, the TB treatment success rate for the cases notified in 2014 was 83%, which is less than what was reported in 2013 (87%). In SEAR, the TB treatment success rate is reported to be 79%. This is mainly due to large-

scale notification in the private sector and related increasing cases 'not evaluated'.

Globally in 2015, there were as estimated 580 000 incident cases of MDR and Rifampicin Resistant (RR) TB. An estimated 250 000 people died of MDR-TB in 2015. The number of MDR-TB cases detected (124 990) worldwide represented just 37% of the 340 000 MDR/RR-TB estimated cases among pulmonary TB cases notified in 2015 and only 21.5% of the incident cases of MDR-TB.

In SEAR, the estimated incidence of MDR/RR-TB was 200 000. MDR/RR-TB cases estimated among notified pulmonary cases in 2015 were 110 000 out of which 35 953 cases were laboratory confirmed. Out of the laboratory confirmed, 32 648 started on treatment.

Globally only 52% of MDR-TB patients were successfully treated and 49% in SEAR.

Extensively drug-resistant TB had been reported by 117 countries globally and six countries in SEAR by 2015.

In 2015, people living with HIV accounted for 1.2 million (11%) of all new TB cases estimated at 10.4 million. In SEAR, an estimated 227 000 cases (4.7%) of the 4.7 million incident cases were HIV positive. In SEAR, an estimated 74 000 cases died of HIV-associated TB in 2015.

Globally, 54% of notified TB patients had a documented HIV test result in 2015. Among HIV positive TB patients notified globally in 2015, 78% were on ART as were in SEAR.

GDI and rGLC mechanism to support MDR-TB scale-up

The adoption of the WHO End TB Strategy by the World Health Assembly (WHA) in 2014 and the inclusion of "ending the TB epidemic" as a target within the health-related Sustainable Development Goal (SDG) 3 by the United Nations General Assembly in 2015 brings with it global commitment to intensify the fight against TB as a leading infectious disease killer worldwide.

The End TB Strategy includes a vision, a goal and three high-level indicators with corresponding targets for 2030 and 2035 and milestones for 2020 and 2025. The 2035 targets are to reduce the TB incidence rate by 90% to 10 cases per 100 000 population per year and to reduce the absolute number of TB deaths by 95% compared with a baseline of 2015. They correspond to the overall goal of ending the global TB epidemic by 2035. The 2030 targets (reductions of 80% and 90% respectively compared with 2015) correspond to the end date of the post-2015 UN SDGs. The third high-level target is the elimination of catastrophic costs faced by TB-affected families; this target is to be achieved by 2020.

The Global drug-resistant TB initiative (GDI) was launched in January 2014 with its mission to serve as a multi-institutional, multi-disciplinary platform organizing and coordinating the efforts of stakeholders to assist countries to build capacity for PMDT in the public and private sectors. The ultimate aim is to provide universal access to care and appropriate treatment for all drug-resistant TB patients.

The Regional Green Light Committee (rGLC) has been charged with decentralization of GLC activities to the regions since 2011/2012. It is supported by the secretariat housed in the WHO Regional Office. Some of the roles of South-East Asia (SEA) rGLC are to review and provide inputs to the regional strategies and/or action plans for the scale-up of PMDT; review and analyse PMDT/r-GLC monitoring mission reports and surveillance data (includes online process during circulation of reports); provide inputs to donors/funding agencies on their request on country PMDT scale-up plans and the subsequent technical assistance needs; oversee the provision of supportive monitoring missions and technical assistance missions to countries, etc.

The SEA rGLC secretariat issues call for membership to the rGLC for experts representing various constituencies, manages the process of replacement of members and potential conflict of interest issues, convenes and provides administrative and logistical support for the r-GLC meetings, maintains records and minutes of the r-GLC meetings and decisions, provides the r-GLC feedbacks to countries/programmes and projects, etc.

Psychosocial and physical rehabilitation of DR-TB patients (remote presentation)

The minimum duration of treatment for drug-susceptible TB is 6 months. Treatment for drug-resistant TB can be anywhere between 18 and 24 months. In some cases, treatment can last for more than 5 years. Despite this, little attention is given to the social, psychological and economic impact this extended treatment can have on the lives of the individuals.

The End TB Strategy that calls for ending TB by 2035 and the one of the key targets of the strategy is "No affected families face catastrophic costs due to TB". Research has shown that despite diagnosis and treatment being provided for free, most individuals have to face high out-of-pocket expenditure on transport, additional medication, nutritional supplementation, etc.

In most national programmes, pre-treatment counselling is not included. This means that those affected are not prepared for the implications in terms of time, money and physiological effect that their treatment can have.

The Global plan to End TB is based on reaching 90% of the key populations, but we fall short on this. Less than 40% of estimated DR-TB patients could be reached, while treatment success for MDR-TB remains low.

Further, there are no known systems set up in most countries among the Region to anticipate for financial loss during lengthy treatment. Returning to jobs or to their education is a challenge as many workplaces and educational institutions do not provide for extended periods of leave or absence.

Robust systems and mechanisms need to be in place for post-treatment rehabilitation and need to be designed based on the needs of those affected. Peer-to-peer counselling can be a low-cost high-impact strategy to address some of these issues. Institutional provisions, under the national response in each country, must be put in place if individuals are to successfully complete treatment and return to their normal lives.

Global Drug Facility support for Drug-Resistant TB Control

Global Drug Facility (GDF) is an initiative of the Stop TB Partnership (2001), mainly funded by USAID, hosted in UNOPS and managed by the Partnership secretariat.

GDF acts as an operating mechanism to facilitate world-wide, equitable access to TB medicines and diagnostics across both public and private sectors. As of December 2015, there are 137 countries that benefited from the GDF procurement/bundled mechanism and US$ 1.44 billion of TB commodities procured since GDF inception in 2001.

Bedaquiline (bdq) is available through the USAID Bedaquiline Donation Program, free-of-charge to eligible countries and all The Global Fund financed countries, while for Delamanid (Dlm) over 100 countries globally eligible for TB financing by the Global Fund can access Dlm via the GDF.

Recent developments on the impact on WHO recommendations on shorter regimen for MDR-TB have resulted on the impact on the cost reduction of treatment regimens and difference in numbers of pills per patient.

Countries that opt for introduction of shorter treatment regimen (STR) will have to prepare a transition plan, including a procurement and supply management (PSM) plan, which includes preparation phase of shifting from conventional regimen to STR.

The preparation phase consists of the following: development/update guidelines and strategies, medicines forecasting and quantification, assess and prepare capacity for diagnosis (LPA, DST), training and update of information systems.

The speaker presented different options of the transition plan, based on uptake policy of each country, proportion of patients eligible for STR, availability of 'old' medicines, and so on.

For TB medicine, the supply chain cycle through GDF lead time is on average 4 to 6 months.

Quantification and early warning system includes regular monitoring of medicines stock balances, and ability to track stock orders and identify potential problems. Currently existing tools available for this purpose are OMS and QuanTB.

The GDF Order Management System (OMS) for countries who procured through GDF and QuanTB was developed by USAID and SIAPS for countries such as Bangladesh, Indonesia, Myanmar, Nepal and Sri Lanka.

Three GDF regional technical advisors (AFRO, EURO, SEAR/WPRO) provide support and capacity-building on all aspects of drug management, such as forecasting, quantification, order planning, early warning, supply decision-making, targeted technical assistance in PSM, etc.

TB Diagnostics: An Overview of Current Recommendations (Remote presentation)

Early diagnosis of tuberculosis, including universal access to drug susceptibility testing, and systematic screening of contacts and high-risk groups is one of the key interventions from the first pillar of 'Integrated, patient-centred care and prevention' in the End TB Strategy.

WHO's recommended techniques for diagnosing TB include microscopy (conventional and LED fluorescent microscopy), culture (solid and liquid), drug-susceptibility testing (FL, SL and non-commercial methods), molecular testing (LPA for FL and SL, TB-LAMP, Xpert MTB/RIF assay) and LF-LAMP urine test for PLHIV.

Culture-based DST (phenotypic) methods for the diagnosis of DR-TB are based on assessment of the ability of *M. tuberculosis* to grow in culture media (solid or liquid) containing a critical concentration of specific anti-TB agents (which indicates resistance) or, conversely, its inability to grow in the same media (which indicates susceptibility).

The indirect proportion method is the most common method used. Resistance is defined when at least 1% of growth is observed at the critical concentration of the drug in the culture medium.

Commercial liquid culture systems for DST reduce the time to result to as little as 10 days, compared with the 28–42 days needed for DST using solid media.

Phenotypic DST for FL agents (isoniazid and rifampicin) and selected SL anti-TB drugs (kanamycin, amikacin, ofloxacin, levofloxacin) are generally reliable and reproducible. While for new and repurposed drugs for MDR-TB treatment – such as bdq, dlm, linezolid, clofazimine – DST methods need validation.

Molecular (genotypic) methods detect specific DNA mutations in the genome of the *M. tuberculosis,* which are associated with resistance to specific anti-TB drugs. Molecular methods have considerable advantages for PMDT, in particular with regard to their speed, the standardization of testing, their potentially high throughput and the reduced requirements for laboratory biosafety.

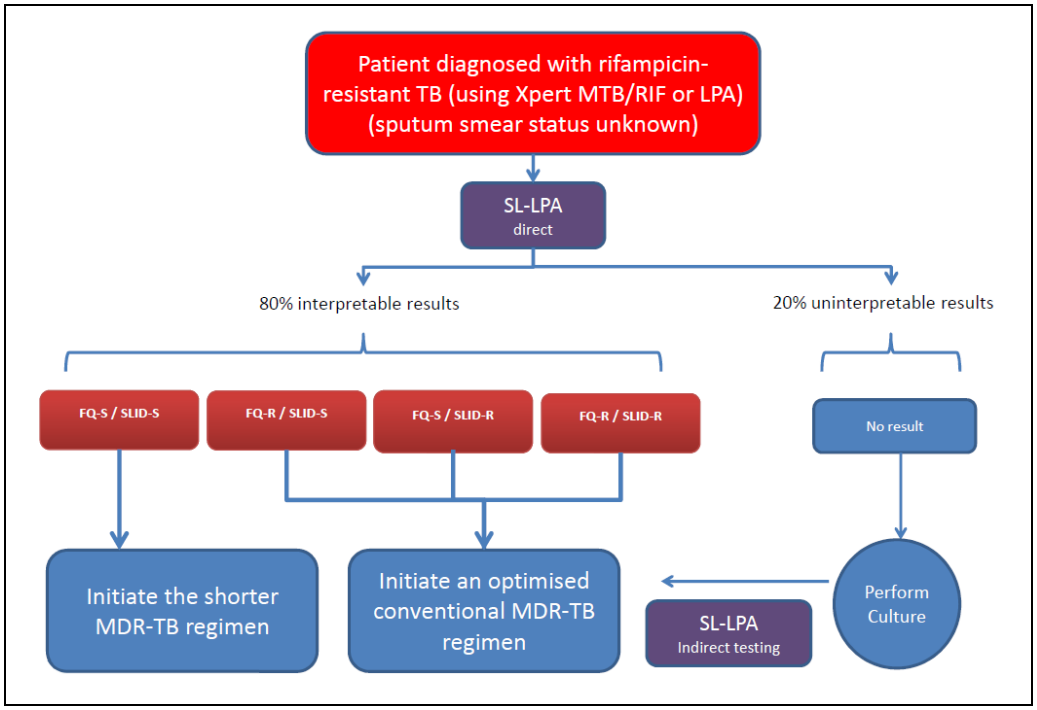
Molecular tests for detecting drug resistance to rifampicin alone or in combination with isoniazid have been recommended for use by WHO since 2008.

Xpert MTB/RIF, as one of molecular diagnostic tools recommended by WHO, should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in all adults presumed to have MDR-TB or HIV-associated TB.

On policy updates on LPAs, two new assays: the version 2 of the Hain Lifescience MTBDR*plus* assay, and the Nipro NTM+MDRTB detection kit 2 (Nipro Corporation, Tokyo) are now available commercially. Both assays show equivalence to Hain version 1. New guidance recommends the use of LPA as the initial test for the detection of resistance to rifampicin and isoniazid in sputum smear – positive specimens and cultures of MTBC.

For second-line LPAs, WHO recommends the use of the SL-LPA for patients with confirmed rifampicin-resistant (RR) TB or MDR-TB as the initial test to detect resistance to fluoroquinolones and the second-line injectable drugs, instead of phenotypic culture-based drug susceptibility testing (DST). A testing algorithm that could be adopted by countries in provided in Figure 1

Figure 1: *Proposed testing algorithm for the second-line lineprobe assay (SL-LPA)* [2]



The Lateral Flow-Urine Lipoarabinomannin assay (LF-LAM) as the latest diagnostic tool is recommended to help the diagnosis of TB in two specific population groups: HIV positive adult in-patients who have signs or symptoms of TB and CD4 cell count less than or equal to 100 cells/μL or PLHIV, and/or HIV positive patients who are "seriously ill" regardless of CD4 count or if the CD4 count is unknown.

However, this diagnostic tool is not recommended by WHO for TB screening of diagnosis of active TB disease in most population groups.

On the Loop-mediated Isothermal Amplification Assay (TB-LAMP), WHO recommends that TB-LAMP may be used as a replacement for sputum smear microscopy for the diagnosis of pulmonary TB in adults with signs and symptoms consistent with TB. TB-LAMP may be used as a follow-

[2] *Based on the presentation made by Dr Chris Gilpin/GTB/WHO*

on test to smear microscopy in adults with signs and symptoms consistent with pulmonary TB, especially when further testing of sputum smear-negative specimens.

These recommendations came with remarks that TB-LAMP should not replace the use of rapid molecular tests that detect TB and resistance to rifampicin, especially among populations at risk of MDR-TB. These recommendations apply to settings where conventional sputum smear microscopy is able to be performed and in testing sputum specimens from patients with signs and symptoms consistent with pulmonary TB. Due to limited evidence, it is unclear whether TB-LAMP has additional diagnostic value over sputum smear microscopy for the testing among PLHIV with signs and symptoms consistent with pulmonary TB. These recommendations are also extrapolated to the use of the TB-LAMP assay in children, based on the generalization of data in adults, while acknowledging difficulties in the collection of sputum specimens from children.

Achieving early diagnosis and universal access to DST requires rapid molecular diagnosis at the first entry point to the health system; all bacteriologically confirmed cases require a rapid DST (at least rifampicin); all rifampicin-resistant TB or MDR-TB require rapid SL-DST (SL-LPA), conventional microscopy and culture required for monitoring TB patients' response to therapy. And all these require a functional laboratory network with strong sample referral mechanism.

While responding to queries, it was clarified that the GeneXpert Ultra cartridge is expected to be available in Q1, 2017. The use of cartridges would be discussed by the experts' group meeting organized by WHO in January 2017.

Dr Gilpin also clarified that the process for establishing the critical concentration for bdq, which is essential for culture-based DST, is ongoing and is expected to be finalized in 2017. The new treatment guidelines also advocate for the need of concurrently developing SL LPA capacity to enhance the diagnosis accuracy and improve treatment outcome, although this may not be essential initially when a low level of resistance to second-line injectable and fluoroquinolone is already known.

Updates – GF perspective on PMDT expansion and role of rGLC mechanism

The proportion and amount of funding available for MDR-TB have increased through allocation, reprogramming and reinvestment of savings. The Global Fund has contributed to the scale-up of DR-TB response globally and in the South-East Asia Region. Patients with DR-TB treated by GF-supported programmes increased from 64 000 in 2012 to 270 000 in 2015. Grants contribute to the scale-up of ambulatory and patients-centred treatment.

Countries have been accessing GF funding for the introduction of new drugs following WHO recommendations as well as the introduction of bdq and dlm, establishing/strengthening drug-safety monitoring, laboratory support, companion drugs and patients support, capacity-building and technical assistance. Countries receiving bdq through the donation programme are reprograming funding to support other TB/MDR-TB activities depending on their needs and priorities.

For the introduction of shorter regimen, GF has financed the introduction of STR as part of operational research in several countries (mostly in Africa). The majority of countries has incorporated the introduction of a shorter regimen in their NFM request. Currently, countries are reprogramming their grants/savings to introduce and scale up a shorter regimen following recent WHO recommendations.

In addition to funding TA through grants, GF provides support for all rGLCs as part of the MOU between GF and WHO. The agreement was revised and its term extended until December 2016. Key changes/features include country ownership and demand driven, differentiated contribution and technical support, contribution to overall TB and DR-TB, including introduction of new diagnostics, new drugs and regimens, performance-based and quality assured technical support, improved financial flow and reporting, strengthening coordination and collaboration with partners, and implementation and follow-up of recommendations of rGLC missions.

Countries are encouraged to further explore and benefit from opportunities within the GF support to scale up new tools, drugs and regimens by using the flexibility within NFM, leveraging support from other sources, including domestic, reprogramming/reprioritization of grants, and

reinvestment of savings and efficiencies as part of continuation of existing grants or new requests.

Clarification was sought by participants on continuation of support for rGLC as it ends in December 2016. Members were not sure whether this support will continue. It was informed that discussions on the subject have happened with WHO and partners but there is no final decision yet from senior management. However, they have acknowledged that rGLC has been useful and countries benefited from rGLC activities.

Main PMDT indicators: WHO South-East Asia Region

The speaker presented an update for South-East Asia countries' data on DR-TB surveillance, coverage of DST, detection of MDR/RR-TB, enrolment on MDR-TB treatment and outcomes for SL treatment.

WHO has been collecting surveillance data on drug resistance globally for TB, which began in 1995 to date. TB data are available to inform policy-makers and to optimize its use for strategically developing effective policies.

After 2009, the WHA resolution agreed on universal access to DST. However, coverage of DST is still low in many countries in South-East Asia and mostly used for retreatment of TB cases. This has important bearing on case detection and the appropriate use of SLD. Data from Bangladesh showed high resistant of pyrazinamide among RR-TB cases (37%).

A total of 16 countries globally have established GeneXpert as the first test for all kinds of TB. Since GeneXpert was introduced on 2012, coverage of DST for RR-TB in SEAR has improved significantly.

Coverage of DST to second-line agents (FQ and SLI) is very low in the largest countries of South-East Asia. This may be related to incomplete data collection from labs and it has implications for patient triage on the shorter or conventional MDR-TB regimens. Detection of MDR/RR-TB cases eligible for SLD has generally increased since 2009 but is still below target in many countries.

Enrolment on MDR-TB treatment has progressed steadily, although compared with the estimated burden, it remains far from the target. Regional trends are heavily influenced by those in India and Indonesia.

Enrolment of XDR-TB is progressing; however, the delay to starting treatment and the shortage of adequate regimens are (with new drugs) likely to be common.

The WHO-recommended shorter MDR-TB regimen may improve outcomes in many patients who are eligible to receive the regimen. Early findings from observational studies in Bangladesh and elsewhere show good outcomes. SL LPA roll-out will be key to further expansion of the shorter MDR-TB regimen.

Some programmes have introduced bedaquiline and delamanid in an effort to improve the effectiveness of their MDR/XDR-TB regimens.

WHO Guidelines for The Treatment of DR-TB, 2016 Update

The speaker presented the latest update on WHO guidelines for the treatment of drug-resistant tuberculosis. Key changes according to these guidelines are as follows:

- A shorter MDR-TB treatment regimen is recommended for RR-/MDR-TB patients, under several conditions (Strength: conditional, Certainty of evidence: very low)
- The design of conventional MDR-TB regimens uses different second-line medicines (Strength: conditional, Certainty of evidence: very low)
- Treatment of children with RR-/MDR-TB based on a first-ever meta-analysis of individual-level paediatric patient data for treatment outcomes (Strength: conditional, Certainty of evidence: very low)
- Recommendation on partial lung resection surgery (Strength: conditional, Certainty of evidence: very low)

A shorter MDR-TB regimen (9–12 months instead of 20-month regimen) can be applied for patients with rifampicin-resistant or MDR-TB who have not been previously treated with SLDs, and in whom resistance to fluoroquinolones (FQ) and second-line injectable (SLI) agents has been excluded or is considered highly unlikely.

Recommendation on longer MDR-TB regimen (LMR) – The LMR, used in patients with RR- or MDR-TB, is a regimen with at least five effective TB medicines during the intensive phase, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C. If the minimum number of five effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five. The regimen may be further strengthened with high-dose isoniazid and/or Ethambutol.

Recommendation on LMR applies to adults and children. However, Group D2 has not yet been approved in children and Group B may be avoided in mild disease. All RR-TB cases are to be treated with a recommended MDR-TB regimen, regardless of whether isoniazid resistance is confirmed or not. The detection of resistance to FQ and SLI agents is important for regimen design.

Along with this recommendation, it is essential to implement active TB drug safety monitoring and management (aDSM) to safeguard patient health and contribute to global knowledge about the safety of individual medicines and drug combinations, especially in novel regimens.

A new recommendation on the role of surgery in patients with RR- or MDR-TB is that elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen.

Day 2

Active drug safety monitoring and management (aDSM)

Active TB drug-safety monitoring and management (aDSM) applies to MDR-TB and XDR-TB patients treated with new medicines, such as bdq or dlm; MDR-TB patients enrolled in treatments with novel regimens, such as those much shorter than the ones currently recommended by WHO; all other XDR-TB patients chose the SL treatment (which often includes multiple repurposed drugs).

The safety profile and the ADRs of the first-line drugs and regimens have been well established. The need for aDSM is more for new and

repurposed drugs and shorter regimens due to limited data on adverse events; limited experience in programmatic use, safety in specific patient populations is unclear as well as "off-label" inclusion of some MDR-TB medicines (linezolid, clofazimine).

As per objectives, aDSM is not expected to meet all criteria for conventional cohort event monitoring. The overall objectives of aDSM are to manage risks from drug-related harm and generate standardized aDSM data to inform future policy updates.

These are essential components of aDSM: patients should undergo active and systematic clinical and laboratory assessment during treatment to detect AEs; all AEs detected should be managed in a timely manner, and standardized data should be systematically collected and reported.

Steps to implement aDSM include (1) create a national coordinating mechanism for aDSM; (2) develop a plan for aDSM; (3) define management and supervision roles and responsibilities; (4) create standard data collection materials; (5) train staffs for collection of data; (6) define schedules and routes for data collection and reporting; (7) consolidate aDSM data electronically; and (8) develop (or use existing) capacity for causality assessment, determine rates and detect signals. Steps 4 and 5 are the only essential requirements before patient enrolment.

aDSM is an essential requirement for implementation of newer drugs and regimens. Integrated within PMDT, it should be an opportunity to strengthen the drug safety monitoring systems.

A simple step-wise approach can be done, and it complements the national PV mechanism.

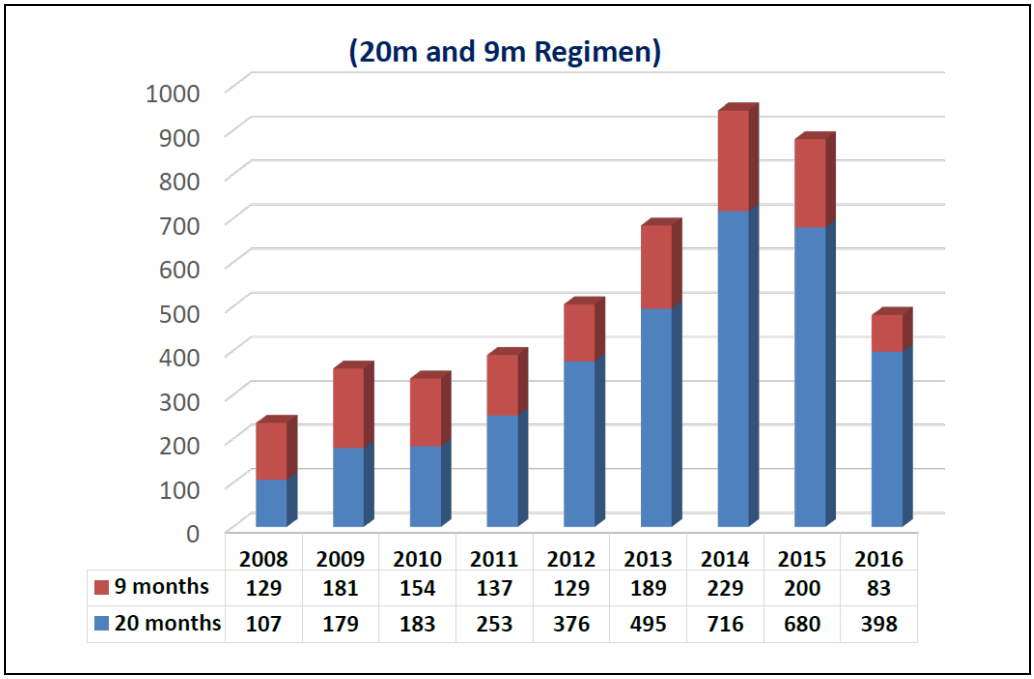
Experience with Implementing shorter regimen of MDR-TB in Bangladesh

MDR TB cases among notified pulmonary TB cases according to DRS 2010–2011 by NTP was estimated about 2100 (1000–3700) among new PTB cases notified in 2015, while among previously treated PTB cases, the number was estimated to be around 2700 (2200–3200).

The proportion of RR-/MDR-TB patients detected compared to the numbers of cases enrolled on treatment has increased over the years – from 70% in 2010 to 93% in 2016 (January–June).

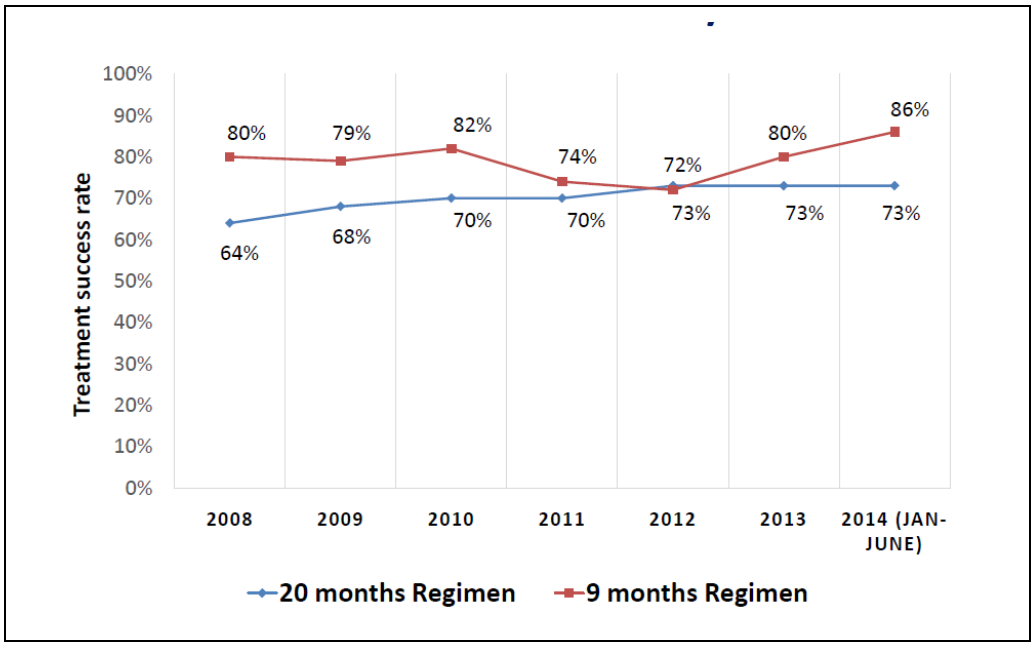
The proportion of RR-/MDR-TB cases enrolled on treatment since 2008 to 2016 is described in figures 2 and 3.

Figure 2: *RR/MDR-TB cases enrolled on treatment*[3]



[3] *Based on presentation made on behalf of NTP, Bangladesh*

Figure 3: *Treatment outcome of RR-/MDR-TB*[4]

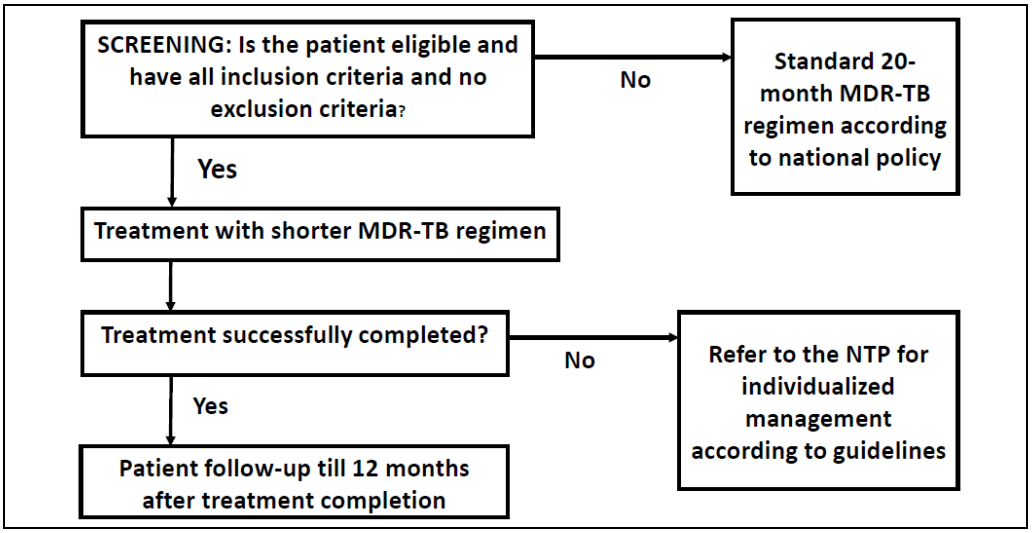


The history of shorter regimen use in Bangladesh began in 1997 since the Damien Foundation initiated treatment of MDR-TB cases. Since then, different combinations of drugs and durations have been tried for development of a short and effective regimen.

Inclusion criteria on current policy for shorter regimen are patients in whom the diagnosis of RR-/MDR-TB has been confirmed by Xpert MTB/RIF or phenotypic DST method, and children and PLHIV on ART. Those who have proven resistance to FQ and Km, more than 1-month previous exposure to SL medicine, intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity, pregnancy or extra-pulmonary disease are excluded for STR. The regimen use policy is described in Figure 4

[4] *Based on presentation made on behalf of NTP, Bangladesh*

Figure 4: *Current regimen use policy: screening, enrolment, treatment and follow-up*



Monitoring of patients on STR includes ECG, creatinine, potassium, LFTs, TSH, glucose, pregnancy test (women), HIV, audiometry, ESR and Hb % during baseline.

And when treatment has started: ECG (monthly), creatinine, potassium, audiometry (monthly while on injectable), LFTs (ad hoc), TSH (month 4), chest X-ray (clinically).

Weekly smear performed until two consecutive smears are negative as follow-up for patients on STR. Then monthly smear and culture during the intensive phase. During continuation phase, smear and culture will be done at the sixth, eighth and ninth month.

A patient who does not smear-convert after 16 weeks will be extended for 4 weeks, and if still not converted by week 20, will be extended for another 4 weeks for a maximum of 24 weeks for the IP.

If still positive on the 24th week, or clinically deteriorating at any time, then she/he will be switched off the STR and placed on an individually design regimen by the PMDT Committee.

The policy on identification and reporting of adverse effects is still in early developmental phase. The adverse effects reporting system is under development. Currently, AEs during hospitalization are managed by a clinical management committee in treatment initiation centres, and AEs during ambulatory phase are initially reported to UHCs; if severe, then patients are referred to specialized centres.

Social support for patients includes monthly incentive for the DR-TB DOT provider, monthly enabler for patient (around US$ 19 per month), support/travel allowance for presumptive cases, patients and accompanied health worker during the ambulatory period for follow-up, cost of baseline and follow-up investigations and providing of vocational training during hospitalization.

The NTP Bangladesh is expected to start scale-up by January 2017 and updating of national PMDT guidelines to incorporate STR is planned.

Bedaquiline implementation in Indonesia

The TB burden in Indonesia was revised after the TB national prevalence survey in 2013/2014 with prevalence rate at 647, incidence rate at 399 and mortality rate at 41 per 100 000 population.

The magnitude of MDR-TB in Indonesia, based on the GTB report in 2015, estimated the number of MDR-TB to be around 5 600 (2%) among new cases and 1100 (12%) among retreatment cases.

The year 2016 is set as one of the milestones toward TB elimination in Indonesia to reach 90% TB incidence reduction and 95% TB mortality reduction in 2035 (compared to 2014 data), as the "TOSS-TB" campaign was launched to set a roadmap for TB elimination; passive, intensified, active, massive case finding strategy; strengthening leadership and regulation; partnership and social mobilization.

Main NTP priorities on PMDT are to expand coverage to achieve universal access for DR-TB patients by 2018 (by expanding the PMDT sites, decentralizing patient care, strengthening district health office, integration to national health insurance, partnerships with NGOs, community for better case finding and services) and to improve treatment outcome (economic

support and social protection, programmatic and clinical supervision, quality of care, service delivery, private sector involvements).

Bedaquiline (bdq) was introduced to provide an alternative drug for highly resistant forms of TB, such as MDR-TB plus resistance to either FQ or SLI and XDR-TB. Standard SLD regimen for pre-XDR and XDR-TB cases was considered not adequate, especially with the failure of MDR-TB treatment. Moreover, the rates of severe side effects and allergy to SLI and quinolones are higher than expected.

The steps that have been taken for bdq pilot implementation plan are 1) country's readiness assessment, 2) identification of partners, 3) establishment of National Task Force and bdq technical working group, 4) development of a national treatment plan for bdq, 5) bdq implementation and 6) generating evidence for scale-up. Steps taken by country to introduce bedaquiline are explained in Figure 5

Figure 5: *Stepwise implementation of bdq in Indonesia (2013–2016)*

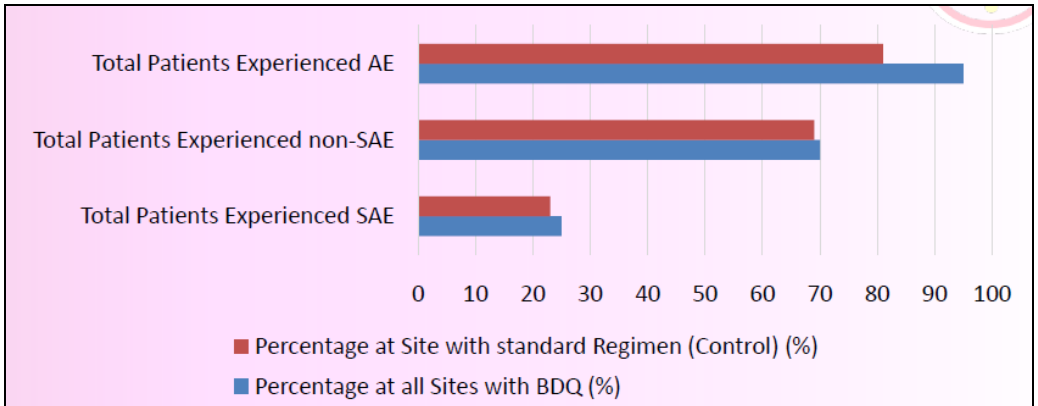
November 2013	Indonesia was appointed as one of 4 countries to implement Bedaquiline treatment (Indonesia, Vietnam, Philippines, Kazakhstan)
June 2014	Workshop of Bedaquiline introduction, followed by PV assessment and site selection
July 2014	First bedaquiline Task force meeting
October 2014	Endorsement of technical guidelines and PV plan by TWG. Global Fund approved budget for Bedaquiline
February 2015	Bedaquiline treatment guideline finalized
April 2015	Pharmacovigilance training workshop: Introduction to Cohort Event Monitoring (CEM)
May 2015	Integration of Bedaquiline PV system in e-TB Manager software
June2015	CEM PV training. Drugs for 50 patients released from customs.
September 2015	First patient enrolment
October 2016	Total 44 patients on treatment

Inclusion criteria used for the enrolment of bdq are: aged between 18 and 65 years, eligible for bdq per indication, signed informed consent and willing to come every day to hospital, while exclusion criteria are prolonged QT, pregnant/breastfeeding woman, PLHIV, chronic liver disease and kidney malfunction.

Case management and social support are ambulatory treatment (for majority of cases) and hospitalization (at least 2 weeks) for complicated patients. Periodical follow-up examinations during baseline and treatment were performed. To ensure treatment adherence, social worker staff were available at hospital, and transport allowance for patients and for home shelter were provided.

Comparison of average total patients experienced an adverse event (AE), serious AE and non-SAE is provided in Figure 6.

Figure 6: *Proportions of adverse events observed among patients on bdq therapy*[5]



NO SIGNIFICANT DIFFERENCE OF AE, SAE AND NON SAE	Percentage at all Sites with BDQ (%)	Percentage at Site with standard Regimen (Control) (%)
Total Patients Experienced SAE	25	23
Total Patients Experienced non-SAE	70	69
Total Patients Experienced AE	95	81

[5] *Based on presentation made on behalf of NTP, Indonesia*

Main challenges faced by NTP include drug registration procedures and sustainability, poor pharmacovigilance system in place, low uptake of new patients on treatment, poor monitoring and information system, limited SL DST and supply chain management issues.

To conclude, bdq introduction is an opportunity for NTP to learn and develop a standard platform for new TB drugs and also a way forward to strengthen the PV for DR-TB as well as TB. Integrated planning, monitoring and evaluation, collaboration and synchronization processes are needed for the existing PMDT system.

Group work: Simulation on transition plan for newer drugs or shorter regimen

(The figures and plans presented in this report are the result of simulation group work at the meeting venue. These should not be used for further distribution or referencing as the actual figures in the official plan of respective countries may vary in certain cases)

Presentation of group work by countries (in order of presentation made at the venue)

rGLC members during one of the the sessions of the meeting.

Participants and observers from the government and other technical partners during a session.

India

Number of cases to be enrolled on shorter regimen in 2017 – 7150 (gradual capacity build-up) and 2018 – 37 200 (@ 60% of all RR TB cases)

Number of cases to be enrolled on bdqand/or dlm – Bedaquiline: 3300 (2017), 7000 (2018) and Delamanid: 80 (2017), 320 (2018)

Activities that need to be undertaken

- Revision of PMDT Guidelines to integrate new initiative
- Capacity-building with decentralized DRTB diagnosis and treatment centres up to district level
- Procurement adjustment and supply chain management
- Funding for NSP 2018–2020
- Expand aDSM

Challenges foreseen in the introduction of

Shorter Regimen:

- Procurement adjustment agreement by GDF and GF, particularly for Clofazimine vs Lfx/Cs

Bedaquiline:

- Capacity-building at national scale for expansion

Delamanid:

- Policy decision on use of dlm
- Regulatory approval time lag
- Guidelines development for use of dlm

Indonesia

Number of cases to be enrolled on shorter regimen	**2017**	**2018**
Presumptive TB (notified in SITT)	1 499 260	1 949 037
Reach of GX	524 741	877 067
TB Positive @14%	73 464	122 789
Rif Resistance @ 8%	5877	9823
All Rif resistance from GX+SSM	6345	10 338
LPA reach (@ 80%)	5076	8270
Pre-XDR + XDR @20%	1015	1654
STR Eligible	4061	6616
STR enrolment@15% ID	3452	5624
STR/XDR enrolment	4467	7278

Steps of implementation of STR and activities that need to be undertaken

- STR start from July 2017
- Using and strengthen the existing system in PMDT
- Regulation of STR has been stipulated in Ministerial Decree
- Ensuring the availability of diagnostic tools (SL LPA) and drugs
- MoU for commitment from stakeholder; who is doing what and how (Local Health Office, Hospitals, Lab, Pharmacies, Social Support, National PV)
- Strengthening Clinical Expert Team
- Monitoring, evaluation and feedback

Challenges foreseen

- Availability and operationalization of GeneXpert machines
- Availability and access to the SL LPA
- Optimization of utilization of SLD that has been ordered
- Capacity-building for implementation of STR

Priority activities in 2017

- Focusing on TB-increase case finding and notification (add 100K by end 2017)
- Preparation of next GF funding proposal by April 2017
- JEMM in January 2017
- District level planning (ongoing)

Nepal

Number of cases to be enrolled on shorter regimen in 2017/2018

2017 = 105				2018 = 200			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
0	35	35	35	50	50	50	50

Number of cases to be enrolled on bdq and/or dlm:

	2017					2018				
	Q1	Q2	Q3	Q4	**Total**	Q1	Q2	Q3	Q4	**Total**
BDQ	0	0	17	17	34	36	36	36	36	144
DLM	0	0	0	0	0	12	12	12	12	48

Activities to be undertaken

- Registration of newer drugs – first quarter of 2017
- Guideline development – first quarter of 2017
- PMDT guidelines and plan finalization and endorsement including
  - Shorter regimen guidelines
  - Construction of regimen with Bdq and Dlm
- Development of aDSM guidelines
- Development of IC guidelines
- HR Capacity build-up (central, regional and district)
- Phase-wise expansion of shorter regimen starting from four sites in 2017 to all DR TC centres in 2018
- Strengthening courier mechanism for sputum samples
- Strengthening social support mechanism for DR TB patients.

Technical assistance required

- Guidelines development
  - aDSM
  - DR TB clinical management for shorter regimen and regimen with Bdq and Dlm
  - Infection control

Thailand

Number of cases to be enrolled on shorter regimen in 2017/2018 is 70 and 520 respectively.

Number of cases to be enrolled on bdq is 80 and no plan so far for dlm. The latter needs discussion.

Activities that need to be undertaken are:

- Approval from MDR Expert Committee
- Policy approval
- NHSO approval for inclusion in package

Challenges foreseen

- Acceptance of international evidence as being relevant to Thai context
- MDR Committee members are very busy and are not able to meet to take decisions
- Capacity within BTB to lead on clinical guideline development and programme implementation
- Thailand plans to transition from GFATM in 2017 – resource planning and inclusion in cabinet budget

TA required: guideline development, guidance on DST on dlm and bdq, support for DRS on SLD Qs:

Day 3

Bangladesh

Number of cases to be enrolled on shorter regimen in 2017 – 500 and in 2018 – 800

Number of cases to be enrolled on Bdq – 250 by 2018 and Dlm – 50 by 2018

Activities that need to be undertaken

- Form a short regimen roll-out working group, chaired by the NTP
- This committee will prepare an overall roll-out strategy
- Decide on a timeline and geographical strategy for roll-out
- Estimate patient number, quantification of medicines for procurement and supply of SLD and other logistics
- Revise algorithm and agree on pharmacovigilance/Update the national clinical guidelines MDR TB, based on the updated WHO guidelines. Outline a pathway for introducing active TB drug-safety monitoring and management (aDSM) in the country
- Prepare laboratory capacity for rapid roll-out. Establish sputum transportation system
- Organize a training curriculum, training schedule and training sessions for professional staff and ancillary personnel
- Prepare a strategy to ensure the availability of the recommended clinical and laboratory tests needed for monitoring the treatment regimen and to monitor for adverse events
- Update reporting and recording formats, including both paper forms and electronic databases for managing MDR patients
- Monitoring and supervision visits to support high-quality programmatic implementation of the MDR/Pre-XDR/XDR TB management

Challenges foreseen

- Infrastructure and maintenance to run Gene X-part machine
- Maintaining cold chain for Gene X-part cartridges
- Establishing Biosafety 3 standards in national reference laboratory
- Development of national guideline for shorter regimen
- Development of national guideline for rapid diagnosis
- Expansion plan and training manual for shorter regimen
- Storage facility for second-line drugs
- Commitment of higher authority
- Sustainable funding
- aDSM development and roll-out

TA required: development guidelines for rapid dx

Democratic People's Republic of Korea

- Number of cases to be enrolled on shorter regimen in 2017/2018: 150 cases will be enrolled on shorter regimen in 2018
- Number of cases to be enrolled on bdqand/or dlm: NA

Activities that need to be undertaken

- Organize study tour on use of PMDT using shorter regimen by the end of this year
- Initiate the testing of second-line LPA when kits arrive – by Q2 2017
- Revise PMDT guideline reflecting new recommendations by Q4 2017
- Ensure funds for procurement of drugs for shorter regimen

Challenges foreseen

- Enhancing the lab capacity for diagnosis of RR/MDR cases, e.g. introduction of second-line LPA, national roll-out of Gene-Xpert system, uninterrupted and continuous procurement of reagents and consumables for C&DST, blood and biochemistry
- Ensuring of funds for procurement of STR drugs
- Optimization of aDSM
- Monitoring of forms
- Consolidation of transportation system for follow-up
- Development of SOPs for transportation of blood samples

TA required from SNRL to NRL for capacity-building SL conventional DST and rGLC mission for support on introducing new recommendations into existing PMDT guidelines

Myanmar

- Number of cases to be enrolled on LMR/STR – 300/240 in 2017 and 3000/2400 in 2018
- Number of cases to be enrolled on bdq / dlm – 30/15 in 2017 and 40/20 in 2018

Activities that need to be undertaken

- Revision of PMDT guideline in progress
- Development of training materials
- Capacity-building and cascade training plan for all health-care providers
- Decentralization in progress
- Strengthening IPC measures and PSM
- Funding secured with GF (2017–2020) in addition to government and 3MDG (Millennium Development Goal 3) funding

- Strengthening aDSM mechanism
- Establishing adequate SL LPA capacity

Challenges foreseen

- Access to SLD LPA and sputum transportation
- Shorter regimen – In line with GF Concept Note (2017–2020) in extensive consultation with national DR-TB expert committee, incorporating recommendations into revised MDR-TB guideline
- Bdq and Dlm – In line with End TB Programme with extensive consultation with national DR-TB expert committee, incorporating recommendations into revised MDR-TB guideline

Technical assistance required for

- Strengthening aDSM mechanism
- Laboratory strengthening, including SLD LPA
- Scale-up electronic R & R (open MRS)
- Development of training materials for new drugs and shorter regimen for all health-care providers
- 4th Nationwide DRS in 2018

5. Review of country mission reports

Indonesia

The PMDT review mission was undertaken from 8 to 14 May 2016. The consultants observed that most of the priority recommendations from the previous mission have either been achieved or are ongoing. Some of the key challenges identified by the mission include the following:

- Weak basic DOTS leading to increase of drug resistance
- Case notification still very low – only 32%

- Too centralized approach with weak district and provincial level leadership and support for TB programme in most instances
- Weak managerial component of the programme: health system, planning and programme evaluation, inadequate HR (quality and quantity) and logistics issues
- Slow PMDT expansion and decentralization of services – there is positive progress and some action has been taken by NTP since the last mission in May 2016
- Focus primarily on re-treatment cases and number of testing among new pulmonary TB cases very limited
- Delays in GeneXpert expansion and its underutilization wherever present; sputum transport a bottleneck
- High loss-to-follow-up: Initial LFU of diagnosed cases not initiated on treatment is around 25% and during treatment LFU is 28%
- Patient support systems are weak and delayed

Key recommendations from the mission:

- Align the diagnostic algorithm to use GeneXpert upfront for all presumptive TB patients
- Decentralize GeneXpert and ensure its efficient use and maintenance
- Increase LPA (FL and SL) and MGIT capacity to meet the expansion requirements
- Enhance case detection in children
- Strengthen TB – HIV linkage (cross-referral)
- Intensified case detection in specific groups and active screening in key affected populations
- Decentralize treatment beyond hospital, puskesmas (PHC) to subdistrict and linking it to decentralized diagnosis

- Treat majority of patients as ambulatory and hospitalization only for severe ADR/complications
- Strengthen infection control in hospitals
- Strengthen mechanism for retrieval of loss to follow up patients
- Consider daily treatment for DS-TB as per international standard of TB case
- Consider shorter WHO-approved regimens for DR-TB in accordance with WHO guideline for the same

Myanmar

The PMDT review mission was undertaken from 3 to 12 August 2016. The consultants observed considerable progress since the last mission.

Some of the key challenges identified by the mission include the following:

- The enrolment of MDR patient remains slow and the gap between diagnosed and enrolled although reduced is still high (21%). The main reasons for this gap include unacceptably long delay from diagnosis to treatment initiation in most of regions/states (~6 weeks) along with patient's refusal to take treatment
- The Xpert capacity remains largely underutilized. With the exception of Yangon, all other Xpert sites are performing less than four tests a day
- The proportion of MDR patients tested for SLD resistance remains extremely low. This leads to delayed diagnosis of pre-XDR/XDR, which may subsequently impact the treatment outcomes as the cohort size expands
- HR remains a challenge with inadequate key staff (lab techs, microbiologists, doctors, team leaders, etc.) at the national, region/state, district and township levels
- Community volunteers are being used as DOT providers, but this remains limited

- Infection control measures are not uniformly applied across all health facilities
- The information system remains paper and manually based. The piloting of the open MRS has been delayed
- Despite the increasing contribution from the GoM, the NTP still relies heavily on external donors, especially The Global Fund (GF).

Key recommendations from the mission:

- Accelerate the enrolment of MDR patients on treatment to meet the targets for 2016–2017
  - Communicate the revised criteria for the presumptive MDR to all the townships and ensure that all eligible patients, as per the criteria, are Xpert-tested
  - Establish a mechanism for line listing and aggressive tracking of all presumptive MDR patients. All townships should report on this indicator quarterly and this should be monitored at district, state/region and national levels
  - Identify and address the reasons for the gap in diagnosis and enrolment
  - Move towards testing of all smear positive cases by second quarter of 2017 in all townships
- Enhance and optimize the laboratory capacity for first and second line DST
  - Undertake a detailed workload analysis of the available Xpert capacity
  - Optimize the use of existing Xpert sites
  - Initiate second-line LPA at the earliest at the labs in Yangon and Mandalay and perform it for all RR/MDR at initiation of treatment. Simultaneously introduce SL-LPA at Taunggyi
  - In the interim continue phenotypic SLDST for FQ and SLI on positive follow-up cultures – Ofx DST to be stopped; do DST for Lfx and Mfx (0.5) only. DST for Eto, Cs and PAS need not be done routinely as the results are unreliable

- The quality assurance mechanism for the labs at Yangon, Mandalay and Taunggyi needs to be strengthened
- Ensure that annual maintenance contracts are in place

➢ Improve management of patients with MDR with and without second-line drug resistance

- Initiate planning for the introduction of shorter regimen after formal concurrence of the National Expert Committee
- Strengthening the aDSM and Pharmacovigilance (PV) mechanism
- Introduce the shorter regimen in Yangon and Mandalay by second Quarter of 2017 and then, based on the experience, scale it up to all the other regions by end 2017
- Ensure the availability of newer drugs (Bdq and Dlm) and repurposed drugs for patients with pre-XDR/XDR and those who are unable to tolerate second-line drugs in the conventional regimen
- The FDA to pursue training in causality assessment and signal detection
- Discontinue PAS in patients that are currently on the drug and manifesting adverse reactions, and to exclude its use in patients for enrolment
- Urgent revision of the MDR TB guidelines based on the changes related to presumptive MDR TB criteria, diagnostic algorithms, treatment regimens, etc.
- Establish community support groups for MDR patients

Nepal

The mission took place from 22-26 August 2016. Progress since the last mission was found satisfactory by the experts.

Some of the key opportunities identified by the mission include the following:

➢ Initiative to transition to the new shorter regimen for DR-TB

- Initiative to use the new TB drugs
- Increased case finding and treatment outcome
- Committed and dedicated health-care workers on some DR-TB sites despites low incentives given
- Efforts are made to close the gaps between estimated and reported cases (operational study)
- Greater community involvement

Key recommendations from the mission:

- Accelerate and safeguard the process of implementation of mandatory case notification, including those from private sectors and endorse strong regulation of OTC sale of anti-TB drugs
- Establish treatment/technical working subgroup in TAG to collect evidences, analyse data and utilize them to formulate policies/SOP for paediatric DR-TB management
- Actively involve community and civil society to bring the services closer for TB/DR-TB patients as the phasing-out of DR-TB planned in upcoming years
- Review drug orders to adjust transition of shorter regimen and use of newer drug for pre-XDR/XDR patients. Consider early GDF mission for better forecasting and quantifying of drugs use
- Develop clear guidelines, checklists, monitoring indicators for supervision, monitoring and evaluation of PMDT services under NTCP for all levels of supervisors and administrators
- Assign and implement DR-TB focal point at all levels
- Develop HR plan that include schedule of training/refreshment course for health staffs that incorporated the latest guidelines/policies, e.g. use of new drug, shorter regiment, infection control, paediatric TB

- Assign IC focal point at all levels to supervise and implement IC measures at all DR-TB health facilities. Review, update and implement the current IC plan according to standards
- Update the PMDT clinical guidelines to indicate how to use the shorter regimen, including modifications to monitoring and reporting

6. Enhancing rGLC support in the Region

Scale up lab and treatment service

The members felt that there is a need to focus on laboratory expansion and appropriate adoption of new tools and technologies for diagnosis of TB and specifically drug-resistant TB in alignment with the PMDT expansion plans. Main challenges in expanding laboratory support include

- Maintenance of infrastructure and equipment
  - Most equipment and infrastructure require careful maintenance, calibration, servicing and repairs
  - Capacity of local vendors in repairing these equipment is minimal
  - Urgent need to identify and build local capacity in handling equipment
- Defining specifications: (infrastructure, equipment and consumables)
  - Policy-makers ensure adequate adherence to established guidelines on safety
  - Enable local vendors to be able to competitively bid for these items
- In-country Standard Operating Procedures aligning with WHO policies
- Accreditation/Certification process:
  - This is critical and most countries have their own policies on this

Possible roles of rGLC in resolving these issues include

- Review the available laboratory infrastructure in countries, including HR availability and assess its adequacy for country needs vis-à-vis the PMDT plan. This can be done either by in-country reviews or circulating questionnaire over email
- Support countries in estimating the laboratory needs for first and second line DST, and accordingly resources needed for the purpose
- Provide technical assistance directly or through a panel of experts to expedite accreditation/certification process
- Provide technical assistance in networking of laboratories within countries

It was agreed by members that mostly the PMDT consultants undertaking the rGLC mission are not laboratory experts. However, they should be able to collect a minimum set of information that could be later used by rGLC members to get the desired picture of ground situation and support country in taking necessary actions.

Synergizing partner efforts for adoption and scale-up of new WHO policy recommendations

rGLC platform is not only about countries and WHO but also consists of partners from various constituencies that include implementers, technical agencies and donors. The rGLC secretariat also continuously interacts with the GDF on issues related to second-line drugs.

It was proposed that for better coordination among all partners in the Region, there is a need for strengthened communication and exchange of relevant information on partner activities. There are PMDT-related training programmes being organized by various partners. If prior information is shared with the rGLC, this could then be used for necessary support to such events, including selection of appropriate participants.

It was suggested by members that it would be good if rGLC could create and update a database of partners and what kind of support they provide to countries in the Region that would help us to map the country's

needs and demands. The PMDT mission report can be utilized to map such needs.

The Director, SAARC TB/HIV centre, informed that there will be a ministerial meeting in December planned to discuss the cross-border issue. The Centre may need support from rGLC in arranging experts, technical inputs into concept note and support while the draft on cross-border migration issue is developed.

Increased availability of rGLC support and visibility

One of the areas recommended by rGLC members for enhanced rGLC activities in addition to the usual monitoring missions is country capacity-building in collaboration with various partners. The members felt that there is a need for uniform training contents across all such activities although methodology adopted by partners may vary. The rGLC secretariat could help disseminate guidelines, training modules/mechanism and other relevant materials, which other countries could adopt.

It was also suggested by members that a 'Nurses network'/consortium needs to be created that will help nurses learn from various settings on how to provide support to patients diagnosed as well as those on treatment. This will help improve adherence to treatment and chances of patients getting cured.

Possibility of a clinical experts' consortium was also discussed. This consortium could be contacted on a need basis to discuss difficult clinical situations and share experiences.

Creating larger pool of consultants

All members felt that there is a need to strengthen the pool of existing consultants available for MDR-TB and related subjects in the Region. The list needs to have two levels of consultants – Experts and junior consultants. The junior consultants could accompany experts for 1–2 missions before taking up individual missions. However, additional funding would be required for the purpose. This will also depend on the MoU extension with the GF or other sources of funding available as well as acceptance of the country where the mission needs to be conducted.

Available ToRs for consultant recruitment should be circulated among rGLC members and they should be able to recommend consultants for either category. rGLC secretariat will undertake/organize screening of the proposed list based on agreed criteria.

Experience sharing with other rGLCs and GDI support

Members stated that a lot of activities have taken place in the Region with support from the rGLC mechanism. Other regions may also have experiences with similar or other new activities that SEA rGLC may not be aware of. Generally, the only forum to share experiences is during the GDI meeting. However, only the chair and sometimes the secretariat get represented in these meetings. There should be more opportunities to exchange thoughts among regions on a wider platform where other members also get the opportunity to participate. This could be a face-to-face meeting for experience sharing, or web-based virtual meeting. Such meetings should be held at least once a year.

Framework on DR-TB response plan

Due to paucity of time, the framework could not be discussed. However, the proposed monitoring indicators have been circulated among rGLC members, and this will be taken further over emails.

7. Conclusion and recommendations

Recommendations for Member States

- Quick roll-out of rapid diagnostics and first-line DST for universal access
- Assessment of needs for second-line LPA and DST and plan for their introduction/roll-out based on country needs
- Organize consultative meetings along with all relevant stakeholders for discussing transition to shorter regimen and prepare a transition plan

- Access to bedaquiline and delamanid needs to be improved in all countries
- Identify areas needing technical assistance, specifically where external technical assistance is required
- Along with introduction of shorter regimen and new drugs, countries to ensure that aDSM mechanisms are in place

Action points for rGLC members

- Additional laboratory networks evaluation questionnaire to be added to SEA PMDT mission reporting template – Dr CN Paramasivan to propose the list
- Create 'how-to' document/practical tips for MDR-TB specifically for nurses. Dr Agnes and Dr Sarin will circulate the available guidelines and training documents respectively. Ms Sirinapha to take the lead in development of this document with support from interested partner organization/s
- To enhance visibility of the rGLC mechanism; editorial/commentary to be considered for publication; Dr Patrick Moonan to take the lead along with the chair of rGLC
- Further discussions are needed on role of rGLC in promoting support and rehabilitation for patients undergoing second-line treatment for drug-resistant TB. Ms Blessina Kumar will lead the discussions

Action points for partners

- For the SAARC TB/HIV centre meeting planned in December 2016, the Director may consider:
- Sharing the concept note of the meeting
- Approach rGLC secretariat and partners for support required
- Share draft policy document under development on cross-border issues in TB management for inputs

Action points for rGLC secretariat

- Draft rGLC survey questionnaires to assess country perception, needs and expectations from the rGLC mechanism to be developed and circulated among rGLC members for comments. This will subsequently be shared with WHO Country Office focal points
- Create database of key partners actively supporting PMDT activities in the Region and update periodically to include any upcoming meetings/trainings/workshops within the Region
- Increase pool of consultants with different technical areas to address the emerging needs of PMDT, e.g. aDSM, Infection Control. Dr Agnes to send ToRs template to members for review and onward circulation to countries. Secretariat to explore with GF/other funding sources regarding possibility of undertaking junior consultant mentoring
- Dashboard on PMDT status to be created to have a snapshot of current status and future plans of Regional countries regarding PMDT in general and specifically roll-out of shorter regimen and new drugs for MDR-TB treatment
- Update rGLC members on a recent topic through Webinar. A suitable timing would be discussed as per everyone's convenience, possibly in early 2017
- Those who are going to Liverpool might develop 1 page to be shared among others who cannot attend the meeting
- Secretariat to initiate discussions with rGLC members on Centre of Excellence (CoE) for PMDT pertaining to the expectation from a CoE in terms of activities, expected basic/available capacity and infrastructure, possible support and certification process
- Discuss with EURO regarding their experience with establishing clinical consultants' consortium and if there are any legal implications or liability issues related to formation of such a consortium

Annex 1

Agenda

1. Opening session
2. Objectives of the meeting
3. Technical sessions
    a. Global and Regional burden of DR-TB
    b. GDI and rGLC mechanism to support PMDT scale-up
    c. Psychosocial and physical rehabilitation of DR-TB patients-challenges and needs
    d. Procurement and supply chain strengthening
    e. Updates to laboratory guidelines
    f. Global Fund perspective on PMDT expansion and role of rGLC mechanism
    g. MDR-TB data Indicators/Regional DR-TB data
    h. Updates to DR-TB treatment guidelines and implementation guidance
    i. Active Drug Safety monitoring and Management (aDSM)
    j. Bangladesh experience with introduction and expansion of shorter regimen
    k. Indonesia experience with pilot use of bedaquiline
4. Group work on introduction of shorter regimen
5. rGLC discussions
    a. Progress since the rGLC meeting
    b. Review country mission reports – key recommendations
    c. Enhancing rGLC support in the Region (round table discussions)
    d. Scale-up of laboratory and treatment services
    e. Synergizing partner efforts for adoption and scale-up of new WHO policy recommendations

f. Increased availability of rGLC support and visibility

g. Creating larger pool of consultants

h. Experience sharing with other rGLCs and GDI support

6. Next Steps: rGLC SEARO activities
7. Conclusions, Recommendations and closing

Annex 2

List of participants

Members

Dr Agnes Cornelle Gebhard
Senior Consultant
Team Leader ACCESS CARE Team
KNCV Tuberculosis Foundation
The Haque, The Netherlands

Dr Patrick Kevin Moonan
Senior Epidemiologist
U S Centers for Disease Control and Prevention
Center for Global Health
Division of Global HIV and Tuberculosis
Atlanta

Dr Asif Mujtaba Mahmud
Associate Professor, Respiratory Medicine
(against the post of Principal Scientific Officer, Biostatistics)
Institute of Epidemiology, Disease Control & Research (IEDCR)
Mohakhali, Dhaka, Bangladesh

Dr C N Paramasivan
Senior Scientific Advisor
FIND India
Chennai, India

Dr Rohit Sarin
Director
National Institute of Tuberculosis and Respiratory Diseases
Mehrauli Road
New Delhi, India

Dr Sarabjit Chadha
Deputy Regional Director
The Union South East Asia Office
C-6, Institutional Area
New Delhi, India

Dr Si Thu Aung
Deputy Director
National TB Programme Manager
Department of Public Health
Myanmar

Ms Sirinapha Jittimanee
Public Health Officer
Bureau of Tuberculosis
Ministry of Public Health
Bangkok, Thailand

WHOCC

Dr Sarat Chandra Verma
Director
SAARC TB and HIV Centre
Thimi, Bhaktapur
Kathmandu
Nepal

NTP Managers and MDR-TB focal persons

Dr Afzalur Rahman
DPM(Training)
TB Control, DGHS
Government of the People's Republic of Bangladesh
Ministry of Health and Family Welfare
Mohakhali, Dhaka
Bangladesh

Dr Choe Kum Sung
Official
Department of TB and Hepatitis
Ministry of Public Health
Pyongyang
Democratic People's Republic of Korea

Dr Ko Jin Hyok
Researcher
National TB Institute
Ministry of Public Health
Pyongyang
Democratic People's Republic of Korea

Dr Asik
National Tuberculosis Program Manager
Directorate of Communicable Disease Control
Directorate General Disease Control and Environmental Health
Ministry of Health
Republic of Indonesia

Dr Endang Lukitosari
Focal Point of MDR-TB
National Tuberculosis Program
Ministry of Health
Republic of Indonesia

Dr Bikash Lamichhane
Director
National Tuberculosis Centre
Government of Nepal
Ministry of Health
Kathmandu, Nepal

Dr Mohan Kumar Prasai
Senior Consultant Chest Physician
National Tuberculosis Centre
Government of Nepal
Ministry of Health
Kathmandu, Nepal

Ms Saijai Smithtikarn
Medical Technologist
Professional Level
Bureau of Tuberculosis
Department of Disease Control
Nonthaburi, Thailand

Observers

Mr Ari Nathan
Director
Regional Environment, Science, Technology and Health (ESTH) Office for South Asia
U S Embassy
Kathmandu, Nepal

Mr Jay Pal Shrestha
Regional ESTH Affairs Specialist
Regional Environment, Science, Technology and Health (ESTH) Office for South Asia
U S Embassy
Kathmandu, Nepal

Mr Anil Thapa
Chief, PME Unit
National Tuberculosis Centre
Nepal Government
Ministry of Health
Department of Health Services
Nepal

Dr Naveen Shah
Consultant Chest Physician
National Tuberculosis Centre
Nepal Government
Ministry of Health
Department of Health Services
Nepal

Dr Bhabana Shrestha
Senior Medical Officer
GNENTUP, NATA
Ministry of Health
Department of Health Services
Nepal

Dr Pramod Raj Bhattarai
DRTB Medical Officer
DR TB Unit
Ministry of Health
Department of Health Services
Nepal

Ms Kamala Wagle
Public Health Nurse Officer
DR TB Unit, NTC
Ministry of Health
Department of Health Services
Nepal

Facilitator

Dr Zaza Y Munez
Regional Technical Advisor
Global Drug Facility Team
Stop TB Partnership
Geneva, Switzerland

Facilitator – remote presentations

Ms Blessina Kumar (rGLC member)
Health Activist and Public Health Consultant
CEO (Interim) Global Coalition of TB Activists

Dr Mohammed Yassin
Senior Advisor, Tuberculosis
The Global Fund
Geneva, Switzerland

Dr Chris Gilpin
Scientist
Laboratories, Diagnostics & Drug Resistance/GTB

WHO Secretariat

WHO/HQ

Dr Ernesto Jaramillo
Medical Officer
Laboratories, Diagnostics & Drug Resistance/ GTB

WCO focal points

Dr Vikarunnessa Begum
National Professional Officer (Tuberculosis)
WHO Country Office
Bangladesh

Dr Malik Parmar
National Professional Officer (MDR-TB)
WHO Country Office
India

Dr Muhammad Akhtar
Medical Officer (Tuberculosis)
WHO Country Office
Indonesia

Dr Nihal Singh
Medical Officer – CDS
WHO Country Office
Nepal

Dr Prakash Ghimire
National Professional Officer
WHO Country Office
Nepal

Dr Keshav Yogi
National Professional Officer
WHO Country Office
Nepal

Dr Ashish Shrestha
National Consultant – TB Program
WHO Country Office
Nepal

Dr Mukta Sharma
Technical Officer (TB/HIV)
WHO Country Office
Thailand

WHO/SEARO

Dr Md Khurshid Alam Hyder
Regional Adviser
TB Control

Dr Vineet Bhatia
Technical Officer
TB Control

Dr Martiani Oktavia
Junior Public Health Professional
TB Control

Ms Anita Saxena
Executive Assistant
TB Control

According to the Global tuberculosis report 2016, the estimated incidence of multi-drug resistant and rifampicin resistant tuberculosis (MDR/RR-TB) in the WHO South-East Asia Region (SEAR) was 200 000 cases in 2015. In the same year, 32 648 such patients were started on treatment. Of all the MDR/RR-TB cases initiated on treatment in 2013, only 49% were successfully treated in SEAR.

In response to the need for scaling up the programmatic management of drug-resistant tuberculosis (PMDT) in the WHO South-East Asia Region, a Regional Advisory Committee on MDR-TB, also known as the regional Green Light Committee (rGLC), was established in 2012. The ninth meeting of the WHO South-East Asia (SEA) rGLC was held in Kathmandu, Nepal, on 17–19 October 2016. The key objectives of this meeting were to undertake technical discussions focusing on the uptake and modalities of implementation of the new WHO guidelines on MDR-TB; review progress in implementation of the recommendations of the eighth meeting and; discuss strengthening of the rGLC mechanism.

The three-day workshop consisted of technical sessions on the first day followed by country experience sharing. A group work on formulating an operational plan on transitioning to a shorter regimen was held on the second day along with country presentations. On the third and last day, rGLC members reviewed country mission reports and discussed ways and means of enhancing rGLC support in the Region.

World Health Organization
Regional Office for South-East Asia
World Health House
Indraprastha Estate
Mahatma Gandhi Marg
New Delhi-110002, India

SEA-TB-369