Informal Consultation on Roll-out of the Xpert MTB/RIF Diagnostic Test and Expanding Laboratory Services for TB Control

National Tuberculosis Institute, Bangalore, India
18-20 October 2011

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Abbreviations

AIDS	acquired immunodeficiency syndrome
DNA	deoxyribonucleic acid
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
FIND	Foundation for Innovative New Diagnostics
GLI	Global Laboratory Initiative
HPV	human papilloma virus
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MTB	M. tuberculosis
NTC	National Tuberculosis Centre
NTP	National TB Control Programme
NRL	National Reference Laboratory
PMDT	Programmatic Management of Drug-Resistant Tuberculosis
RIF	Rifampicin
SNRL	supranational reference laboratories
TB	tuberculosis
TB/HIV	HIV-related TB
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

1. Background

The South-East Asia (SEA) Region of the World Health Organization (WHO) has the highest burden of tuberculosis in the world. The Region accounted for about 40% of the global TB burden in 2010. It is estimated that about 3.5 million new cases of TB occurred in 2010 and that about half a million people die of this disease annually, most of them in the five Member countries Bangladesh, India, Indonesia, Myanmar and Thailand. Of the 3.5 million people living with HIV in the Region in 2010, roughly half were estimated to be co-infected with TB. Fortunately, levels of multidrug-resistance (MDR) are still low at around 2.1% among newly detected cases. Among previously treated cases in the Region, the MDR-TB rate is estimated to be higher at around 17%. However, given the large number of TB cases in the SEA Region, this translates into 130 000 multidrug-resistant tuberculosis (MDR-TB) cases.

While good progress has been made with TB control in Member countries of the WHO SEA Region, further improvements in the scope and extent of TB services are envisaged through the application of the wider Stop TB strategy that now forms the basis of the regional and national multiyear plans for TB control, aimed at reaching the TB targets under the MDGs.

Achieving universal case detection and treatment of all forms of TB, expanding services for multi and extensively drug-resistant (XDR) TB and HIV associated-TB requires developing capacity of national laboratory networks to detect all forms of TB, including drug- resistant TB and HIV-associated TB, through quality-assured culture and drug susceptibility testing and deployment of newer diagnostics that are now becoming available. Enhanced laboratory capacity is also required to undertake regular drug-resistance surveillance to determine trends in MDR/XDR-TB.

The development of the Xpert MTB/RIF assay is platform technology that has the potential of being used for screening for infectious and non-infectious diseases, including HIV viral load, malaria, and detection of

human papilloma virus (HPV) for cervical cancer. This TB platform was completed in 2009 and is considered to be an important breakthrough in the fight against TB. For the first time, a molecular test is simple and robust enough to be introduced outside conventional laboratory settings.

Xpert MTB/RIF detects *M. tuberculosis* as well as rifampicin resistance-conferring mutations using three specific primers and five unique molecular probes to ensure a high degree of specificity. The assay provides results directly from the sputum within 100 minutes. On 8 December 2010 the World Health Organization (WHO) endorsed the Xpert MTB/RIF assay — a highly sensitive and specific, automated, real-time molecular diagnostic test which uses state-of-the-art DNA technology — for rapid and simultaneous detection of tuberculosis (TB) and rifampicin resistance (a reliable proxy for multidrug-resistant TB) in both HIV-negative and HIV-positive individuals.

The technology is suitable for use at the district and subdistrict health service level, outside of conventional laboratory settings. Given its ease of use and speed of diagnosis (100 minutes), Xpert MTB/RIF is expected to have a major impact on patient care and disease control by reducing patient and health service diagnostic delays, decentralizing the diagnosis of MDR-TB and HIV-associated TB, and accelerating patient access to appropriate care.

Although technical end-user training requirements for Xpert MTB/RIF are minimal, maximum efficiency and optimal use of the technology requires major overhaul of TB and MDR-TB diagnostic algorithms, changes in patient management approaches, and changes in case definitions and monitoring and evaluation indicators.

Over the years, technical issues relating to smear microscopy, mycobacterial culture and drug susceptibility testing and quality assurance have been streamlined. Regional and national laboratory workshops have been organized and trainings conducted. At the meeting of the National TB Programme Managers of the Region at WHO-SEARO, New Delhi, India, in December 2009, countries requested the assistance of WHO and partners in providing further guidance and support to strengthen laboratory capacity to effectively expand TB diagnostic services including the use of newer diagnostics.

2. Objectives of the Informal Consultation

The objectives of the Informal Consultation on Roll-out of Xpert MTB/RIF Diagnostic Test and Expanding Laboratory Services for TB Control held at NTI, Bangalore, India, on 18-20 October 2011, were to:

(1) review the status and identify the inputs required for expanding the scope of laboratory services in Member countries of the WHO SEA Region;

(2) provide guidance on the components for laboratory strengthening to be included in national TB control plans, including the introduction of newer diagnostics; and

(3) develop plans to meet the required scale-up of laboratory capacity in the Region, including technical assistance, resource mobilization, engaging with other technical partners and strengthening capacity of supranational reference laboratories, to technically support Member States in the Region.

3. Presentations and proceedings of the Informal Consultation

The Informal Consultation commenced with an inaugural address by the Director of the National Tuberculosis Institute on TB epidemiology of India. This was followed by the stating of the objectives of this meeting by Dr Md Khurshid Alam Hyder, Regional Adviser for Tuberculosis Control, WHO-SEARO, New Delhi. This was followed by the first session detailing an overview of TB control activities in the WHO SEA Region. The presentation covered the areas of the global burden of all forms of TB, including TB/HIV, MDR and XDR-TB. It also covered the status of TB control within the South-East Asia Region (Figure 1), the MDR-TB estimates (Figure 2), regional laboratory status, country plans for programmatic management of MDR-TB, challenges and the way forward for engaging all care-providers, introductions of newer diagnostic tools to improve PMDT and drug logistics and role of WHO in technical assistance to the Member States.

Figure 1

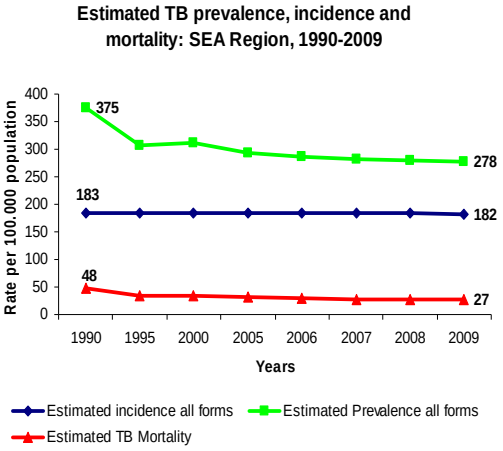


Figure 2

Countries	Among New Smear+ (NSP) cases	Among previously treated cases
Bangladesh	2.2 %	14.7 %
India	2.3 %	17.2%
Myanmar	4.2 %	10.0 %
Nepal	2.9%	11.7%
Sri Lanka	0.2 %	17 %
Thailand	1.7%	34.5%

The second presentation addressed the laboratory status with details of current capacity as shown in Table 1. It also identified the gaps and the steps that were required to further build and expand capacity, including the technical and funding assistance that would be essential for scaling up laboratory services especially for the programmatic management of MDR-TB.

Table 1

Status of Laboratory Networks in WHO SEA Region

Activity	Status
Smear Microscopy Network	All countries (QA partial /complete)
National Reference Laboratory	Functional (except Bhutan, Maldives*, DPR Korea, Indonesia** and Timor-Leste)
Linkage to Supranational Laboratory Network	All countries
Culture and DST facility either in NRL or other sectors	All (except Maldives, Timor-Leste)
Introduction of newer tools ongoing in the NTP	India, Myanmar, Bangladesh, Indonesia
Newer tools (Xpert) to be introduced	India, Indonesia
Supranational Reference Laboratories of SEA	TRC Chennai (3) and NTRL Bangkok (4)
Other SRLs	SRL Hong Kong(1), Adelaide (1), Gauting (1) and Antwerp (1)

* Plan for NRL ** 5 Regional Reference labs

The third presentation was on an overview of the Global Laboratory Initiative (GLI) for the strengthening of laboratory services and covered the goals of The Stop TB Partnership and the objectives for setting up the GLI, its composition, the technical partners (Figure 3), the functions of the GLI including the formulation of policy guidelines on the use of new diagnostic tools (Figure 4), the TB CAP tool kit for quality management of laboratories, procurement supply management for laboratories and biosafety issues.

Figure 3

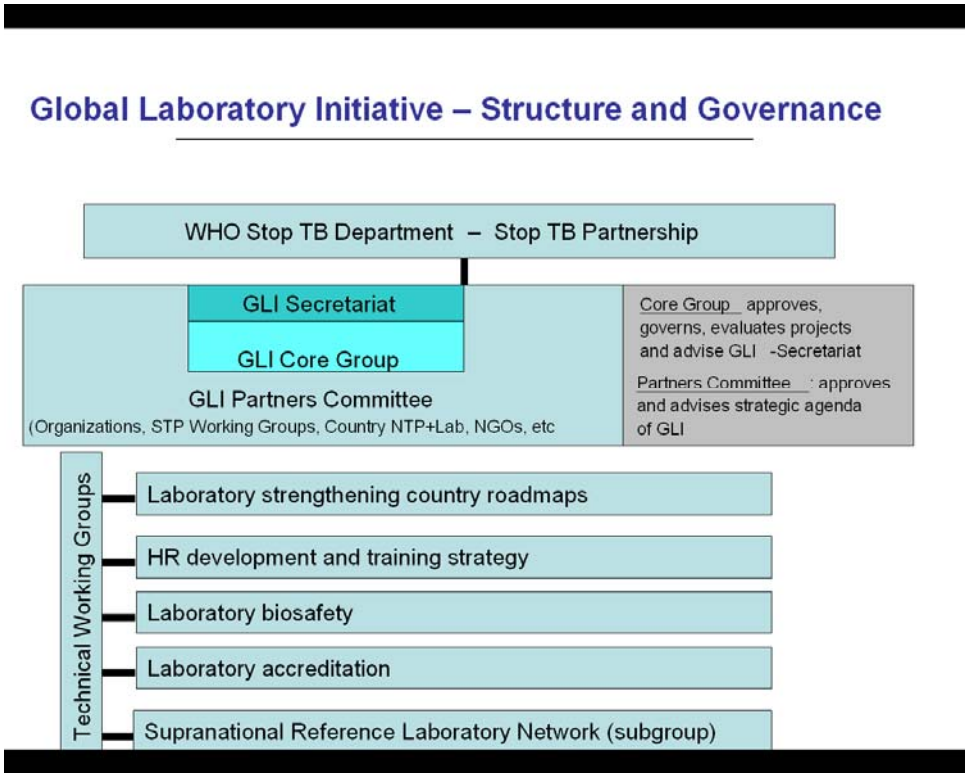
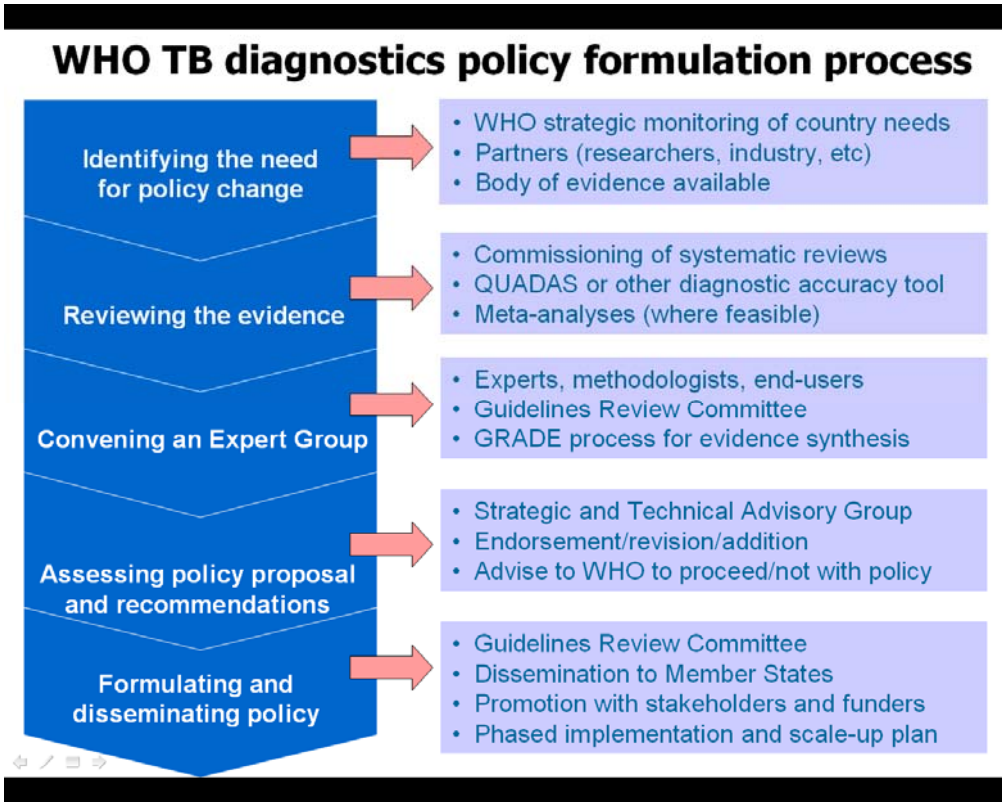
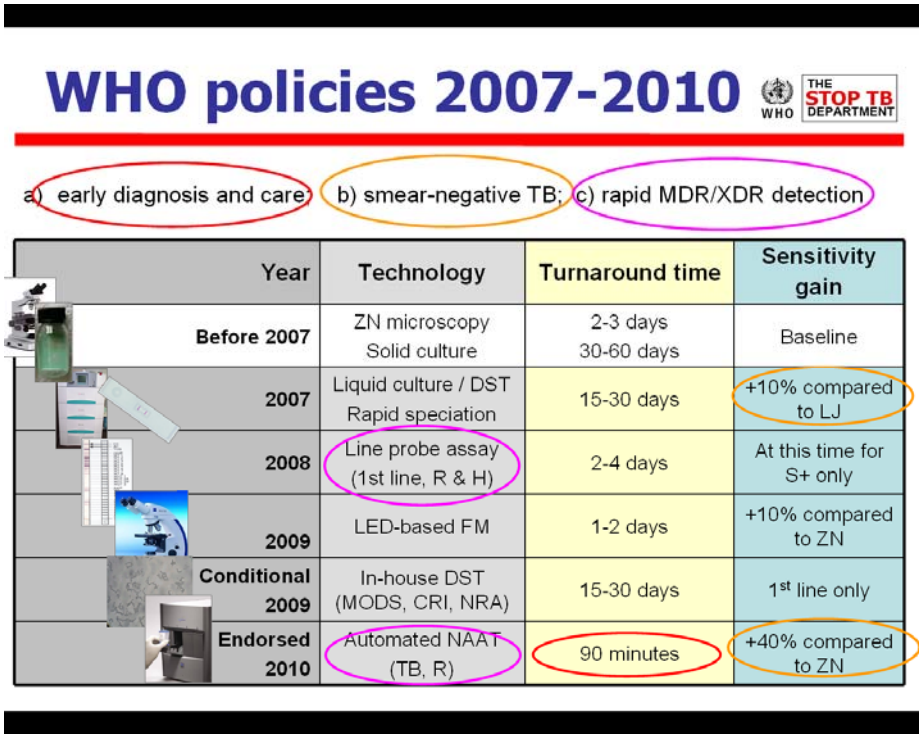


Figure 4



This was followed by a presentation of current WHO policy guidelines (Figure 5) for laboratory strengthening, especially in resource–constrained high-burden TB settings. The presentation covered the roadmap for scaling up laboratory services with strengthening of basic services, and introduction and the use of newer diagnostic tools to scale up laboratory capacity. It also included the algorithms and changes in country policies for the introduction of newer tools within programme settings.

Figure 5



During the post-lunch session a presentation on the Xpert TB RIF system was made that covered the principle of the test, and featured a short video presentation on the working of the cartridge, the sensitivity and specificity of the test, positioning, research studies on use in different countries, the role of Xpert TB in diagnostic algorithms, the evidence base for WHO recommendations on the use of Xpert TB RIF, and the summary recommendations for use of Xpert TB in countries. This was followed by a presentation on the rapid implementation of Xpert test and the practical considerations for use of the test. The presentation covered the site selection, positioning, patient selection, workload, operational considerations, instrument management and other requirements including quality management.

Figure 6

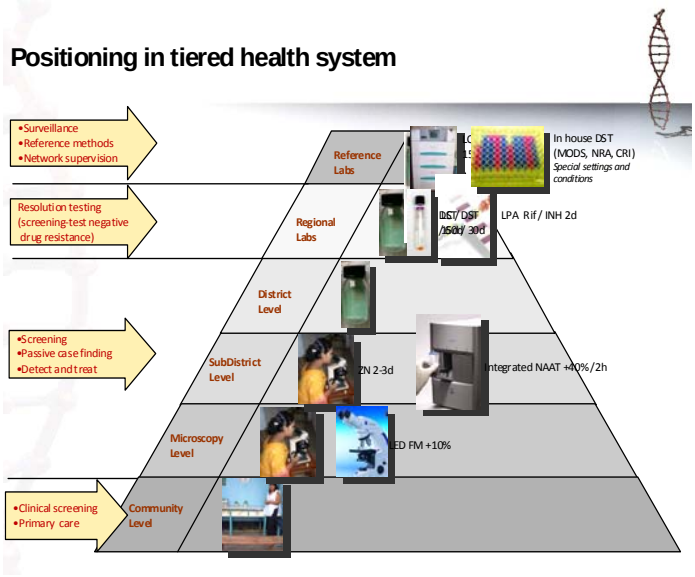
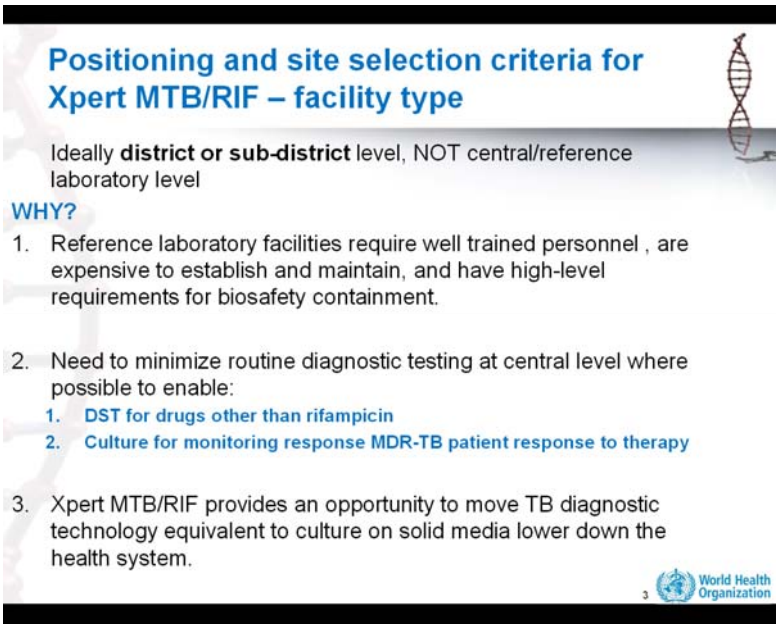


Figure 7



The first presentation on Day 2 was from the Foundation for Innovative New Diagnostics on the EXPAND TBx Project with special focus on the SEA Region. The project is supporting four countries of the SEA Region (Myanmar, India, Indonesia and Bangladesh) for the introduction of newer diagnostic tools line probe assay (LPA) and liquid culture systems. The project has assisted in establishing 2 laboratories in Myanmar and is planning 43 laboratories in India, of which 9 have been established.

In Bangladesh and Indonesia the preparatory visits have been completed and the project will be established in 2011-2012. The project covers the procurement of equipment required for LPA, MGIT liquid culture systems, consumables, reagents and diagnostic kits for the project period, i.e. until 2013. The project is being funded through UNITAID, a corpus fund that collects surcharge on international air tickets sold in Member countries such as France, Brazil and a few other European nations and acts as a donor for procuring quality-assured second-line drugs and newer diagnostics for MDR-TB in identified resource-limited and high-burden countries.

This was followed by country presentations on laboratory status and expansion plans for the next three-five years. The countries were then given templates for filling details of the status of laboratories, expansion plans and introduction of newer tools including Xpert TB RIF. The afternoon was spent in visiting the NTI NRL to brief NRL microbiologists on the laboratory layout for molecular and liquid culture facilities, biosafety issues and conventional bacteriology.

The Day 3 proceedings commenced with presentations by the representatives of the national reference laboratories based on the template provided the previous day. Most countries had a comprehensive national scale-up plan for expansion of laboratory services, including the introduction of newer diagnostics. Smaller countries with low TB burden were not sure about the introduction of newer tools such as molecular tests for rapid identification of MDR TB as they were not included in the list of countries slated for negotiated pricing for procurement of these tools. This was highlighted as part of their presentation and was addressed by the GLI HQ laboratory focal point.

The meeting concluded with a presentation of the conclusions and recommendations by the Director, National Tuberculosis Institute, Bangalore, and a vote of thanks.

The conclusion and recommendations of the meeting are as follows:

4. Conclusions

While national reference laboratories (NRLs) in Member countries (with the exception of Maldives and Timor-Leste) now have the capacity for mycobacterial culture and DST, the capacity of other countries except Thailand needs upgradation. The NTRLs in Bangladesh, Indonesia and Myanmar have recently been quality assured for culture and DST, while Sri Lanka is undergoing the process of accreditation by supranational reference laboratory (SRL), Chennai. In Nepal, these services are being primarily provided by a quality-assured NGO laboratory which has been supporting the country for culture and DST for over 15 years. However, the National Reference Laboratory at the National Tuberculosis Centre (NTC) has commenced providing services and the SAARC TB and HIV/AIDS Centre, Kathmandu, Nepal, is in the upgradation phase. Bangladesh is also being supported for culture and DST services by NGOs. In addition the National Tuberculosis Reference Laboratory (NTRL), Dhaka, has also initiated diagnostic services for the programmatic management of drug-resistant tuberculosis (PMDT).

The National Institute for Research in Tuberculosis (formerly TRC), India and the national TB Reference Laboratory, Thailand, which are also WHO-designated supranational reference laboratories for the Region, perform second-line DST (SLDST), in addition to the two other NTRLs in India (National TB Institute, Bangalore and LRS Institute, New Delhi). All of these participated in proficiency testing (including SLDST) with the WHO-coordinated SRL at Antwerp, Belgium.

The Xpert MTB/RIF assay is a cartridge-based nucleic amplification technology that has the potential for screening infectious and non-infectious diseases, including HIV viral load, malaria and detection of HPV for cervical cancer. The TB platform was completed in 2009 and it is considered an important breakthrough in the fight against TB. The assay provides results directly from sputum within 100 minutes. On 8 December 2010, WHO

endorsed the Xpert MTB/RIF assay, a highly sensitive and specific, automated, real-time molecular diagnostic test that uses state-of-the-art DNA technology for rapid and simultaneous detection of tuberculosis (TB) and rifampicin resistance (a reliable proxy for multidrug-resistant TB) in both HIV-negative and HIV-positive individuals. The technology is suitable for use at the district and subdistrict health service level, outside of conventional laboratory settings.

Given its ease of use and speed of diagnosis, Xpert MTB/RIF is expected to have a major impact on patient care and disease control by reducing diagnostic delays, decentralizing the diagnosis of MDR-TB and HIV-associated TB, and accelerating patient access to appropriate care. Although technical end-user training requirements for Xpert MTB/RIF are minimal, maximum efficiency and optimal use of the technology requires a major overhaul of TB and MDR-TB diagnostic algorithms, changes in patient management approaches, and changes in case definitions and monitoring and evaluation indicators. Also, country-specific validation, sustainability, addressing the basic requirements for optimal utilization, maintenance, annual calibrations, monitoring, mentoring and data management at the country level requires careful planning with the NTP and partners.

The UNITAID-funded EXPAND TB project supports the introduction and scaling up of newer diagnostic tools in identified resource-constrained and high-burden countries. This unique project supports quality-assured second-line drugs for MDR-TB treatment and developing laboratory capacity through Foundation for Innovative New Diagnostics (FIND) for introduction of newer diagnostic tools. The project has been implemented from 2009 and has so far supported 27 such countries in Africa, Eastern Europe and South Asia, including India. India has one of the biggest budgets for the introduction of newer tools for identifying and treating MDR-TB. The project expanded its activities to support Myanmar and two other SEA Region high-burden TB countries, Bangladesh and Indonesia, in 2011.

5. Recommendations

(A) Recommendations for the National TB Control Programme:

- To continue efforts in strengthening NTRLs in capacity-building and appropriate implementation of planned activities.
- To strengthen coordination with the intermediate-level reference laboratories.
- To carefully assess the roll-out of Gene Xpert at different levels while coordinating with partners/private sectors working at the country level.
- To revise/update the laboratory expansion plan in line with newer diagnostics and synchronize with the PMDT expansion plan.

(B) Recommendations for WHO-SEARO:

- To provide technical assistance and liaise with GLI for introduction of newer tools, as well as assistance for the EXPAND TB project in eligible countries.
- To update countries time to time on information on roll-out of Gene Xpert and newer technologies in diagnosis of TB and MDR-TB.
- To optimize and improve coordination of SRL support for NTRLs in South-East Asia and Western Pacific regions.
- To continue limited financial support to SRLs as and when required.

Annex 1

Agenda

(1) Overview and plans for TB control in SEAR

(2) Overview of laboratory networks in SEA Region – situation and needs

(3) Overview of the Global Laboratory Initiative and strengthening TB laboratory services

(4) WHO policy guidelines on the use of new diagnostic tools

(5) Introduction of Xpert MTB/RIF diagnostic test

(6) Rapid implementation of the Xpert MTB/RIF diagnostic test

(7) Technical and operational 'How-to' and practical considerations

(8) Discussions on the use of Xpert TB/RIF by SEAR countries

(9) Expand TB project – current status and plans in SEAR

(10) Country presentations: progress on laboratory network strengthening

(11) Country plans for the use of Xpert MTB/RIF and expanding laboratory services

(12) Discussion on country plans

(13) Conclusions and recommendations

Annex 2

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