Tuberculosis – r-GLC Mission Report: 2018

Democratic Republic of Timor-Leste

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TB r-GLC MISSION REPORT 2018

Programme: Country: Democratic Republic of Timor-Leste

Lead implementing agency:

National Tuberculosis Programme, Ministry of Health, Government of Timor-Leste

Inclusive dates of mission:

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Acknowledgments:

- Ministry of Health, Government of Timor-Leste, Dili
- National TB Programme, Government of Timor-Leste, Dili
- WHO Timor-Leste, Dili and India, New Delhi
- WHO South East Asia Regional Office, New Delhi
- Dr S Anand, WHO-RNTCP National Consultant TB Labs, New Delhi

Contents

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The author would also like to thank Dr Rajesh Pandav - WHO Representative to TL for the invitation and trust to conduct the mission under horizontal collaboration in revision of TB and PMDT guidelines including introduction of newer injection free regimen; Ms Renu Sharma – Administrative Officer & Ms Da Cruz Vicente, Irene Teresa – Executive Officer for providing organizational support; Dr Yu, Dongbao – Technical Officer Epidemiology & Ms Imaculada Lobo Belo – Program Associate (Nutrition & Food Safety) for sharing valuable updates about the National Nutrition Strategy and Nutrition Strategic Review (2017), Dr Dipanjan Roy, Technical Officer – HIV, WHO TL for valuable support, care and time given throughout the mission and sharing information on situation, challenges, potential solutions and way forward for TB and MDR-TB interventions in TL as well as discussion on specific action points for WHO country office to support TL accelerate its response to ending TB. Finally, thanks also to Dr Mukta Sharma – Regional Advisor (TB/HIV/STI/Hepatitis), Dr Partha P Mandal – Technical Officer TB and Dr Vineet Bhatia - Technical Officer MDR-TB at WHO SEARO for their valuable time and guidance on various issues regarding TB and PMDT situation in TL and the way forward.

Abbreviations and acronyms:

ADR	Adverse drug reaction
aDSM	Active drug safety management and monitoring
AIDS	Acquired immunodeficiency syndrome
Am	Amikacin
Bdq	Bedaquiline
CCT	Cooperativa Café Timor
Cfz	Clofazimine
Cs	Cycloserine
Dlm	Delamanid
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment Short-course
DR-TB	Drug-resistant tuberculosis
DRS	Drug-resistance survey
DST	Drug Susceptibility Testing
DRT	District tuberculosis coordinator
EMR	Electronic medical record
EQA	External quality assurance
FLD	First line drugs
GoTL	Government of Democratic Republic of Timor-Leste
GDF	Global Drug Facility
GF	The Global Fund
GLC	Green Light Committee
HIV	Human immunodeficiency virus
IoM	International Organization of Migration
JICA	Japan International Cooperation Agency
KOICA	Korea International Cooperation Agency
Lfx	Levofloxacin
LJ	Lowenstein Jensen
LPA	Line probe assay
LT	Laboratory technologist
LTBI	Latent TB infection
MDR-TB	Multi-drug resistant tuberculosis
Mfx	Moxifloxacin
MoH	Ministry of Health
NGO	Non-governmental organization
NTP	National Tuberculosis Programme
NTRL	National TB Reference Laboratory
Ofx	Ofloxacin

PMDT	Programmatic Management of Drug Resistant Tuberculosis
PMU	Programme Management Unit
PSM	Procurement supply chain management
SAMES	Servisu Autonomi Medicamento Equipamento Saude
SCTS	Specimen collection and transport system
SEAR	South East Asia Region
SISCa	Servisu Integradu da Saúde Communitária (Integrated community health services)
SLD	Second line drugs
SL-LPA	Second line – line probe assay
SMTR	Shorter MDR-TB Regimen
SnF	Saude na familia (Comprehensive service package of primary health care)
SNRL	Supranational Reference Laboratory
TB	Tuberculosis
TL	Democratic Republic of Timor-Leste
TO	Technical Officer
WCO	WHO Country Office
WGS	Whole Genome Sequencing
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis

I. Executive summary:

"I go I die, I stay, I die, better to stay and die in my house" *– health seeking behavior in Timor-Leste.*

Democratic Republic of Timor-Leste is one of the high tuberculosis (TB) burden countries in the South-East Asia Region. Current estimates indicate that TB prevalence and mortality from TB in the country are among the highest in the South-East Asia region. TB kills 100 people per 100,000 people in TL, in spite of TB services being available since nearly two decades. Malnutrition and smoking are the top two known drivers of the TB epidemic synergizing with TB menace to kill people in TL.

The country initiated PMDT services with external support of The Global Fund (GF) since 2008 and technical assistance from WHO Timor-Leste. PMDT services are available across all municipalities of the country under the NTP framework and are currently supported by commodity cum technical support through GF-NFM funding. Other partner organizations like Caritas Dili (Catholic Institution), Klibur Domin (NGO), Bairo Pite Clinic (NGO), International Organization of Migration (IOM), Burnet Institute (Donor and Implementing partner), Café Cooperativa Timor (CCT) Clinic (Corporate Sector partner), Korea International Cooperation Agency (KOICA) and Japan International Cooperation Agency (JICA) have also been supporting TL particularly in active case finding, nutrition support, laboratory expansion, private sector engagement and treatment of TB and DR-TB.

This is the annual monitoring mission for Tuberculosis with focus on Programmatic Management of Drug-Resistant TB (PMDT) component of the National TB Control Program (NTP) of the Government of Timor-Leste (GoTL) and under horizontal collaboration support through WCO TL for revision of TB and PMDT guidelines and the introduction of the new WHO recommended injection free regimen for MDR-TB. The mission was undertaken on behalf of regional Green Light Committee (r-GLC) of World Health Organization - South East Asia Region (SEAR) from 27 – 31 August 2018.

The objectives of the mission were

- To provide technical assistance to update and revise the TB Diagnosis and Treatment Manual of Timor-Leste to align it with many recent WHO recommendations specifically to cover:
  - Newer diagnostic protocols using GeneXpert® / Culture and X-Rays
  - Diagnosis and Treatment of Drug Resistant TB
- To review progress since the last PMDT mission and the DRS implementation
- To provide recommendations on priority bases with timeframes.

The five days long mission covered briefing meetings with key officials of NTP, MoH, and WHO TL, visit to key health care facilities like NTP Office, National TB Reference Laboratory (NTRL) and National Hospital at Dili municipality, Klibur Domin drug-resistant TB (DR-TB) center as well as GeneXpert® laboratory at Liquica municipality and WHO Country Office of TL. During the mission, specific meetings were done with key officials from NTP, Klibur Domin, National Hospital, NTRL and WCO-TL. In parallel, a series of trainings of key laboratory technicians and district TB coordinators on the national TB drug resistance survey (DRS) protocol was facilitated by Dr S Anand, WHO RNTCP National Consultant – TB Labs, New Delhi from 20-31 August 2018 at Dili, Baucau, Aileu and Liquica. The author also joined the training at Liquica and NTRL Dili to review the preparation and deliberate on the national DRS protocol to recommend further refinements.

The activities include comprehensive review of services in terms of patient care, programme management, supervision monitoring systems, community engagement, information communication systems for TB/DR-TB, interactions with key officials, specialists, doctors, technicians, staff, patients, community representatives at the sites visited to analyze the progress made and plans developed for TB and PMDT implementation in light of the last PMDT mission report (Nov 2017), the current national strategic plan and national TB guidelines including PMDT, the PMDT expansion plan and the resolve to adoption of the updated WHO Rapid Communication on treatment of multi drug-resistant (MDR) and rifampicin-resistant (RR) TB (August 2018).

The mission also covered a deliberation at Dili with NTP manager, regional TB coordinators, specialists from National Hospital and WHO staff with special focus on the WHO Rapid Communication on treatment of MDR/RR-TB to review and discuss around the revision of TL's PMDT guidelines to include options of updated integrated TB and DR-TB diagnostic algorithms complemented by active case finding and infection control in out-patient department through cough corners, inclusion of universal DST through GeneXpert® and second line LPA, injection free MDR-TB regimen with inclusion of newer drugs like Bedaquiline, effective management of adverse drug reactions (ADR) including concepts of active drug safety monitoring and management (aDSM).

The key observations and actionable recommendations based on country's shared felt needs, observed facts, figures and available evidences from program data and field visits were shared and discussed in details by the author with the key stakeholders of NTP, MoH and WHO TL.

Findings/Observation

a) Progress from the last mission:

The last mission was held in November 2017. The progress was assessed based on observations made and interactions with key NTP stakeholders of TL.

SN	Priority Recommendations	Progress
1	Universal DST should be achieved as soon as possible. NTP initiate steps in 2018 for phased implementation by 2019	**Partly met**
2	Timely implementation of the planned drug resistance survey	**Not met**
3	Urgently plan for introduction of rapid molecular test for second line DST	**Not met**
4	Coordinate with SNRL for rapid accreditation of national reference laboratory	**Partly met**
5	Prepare a plan with timelines for transitioning to shorter regimen	**Partly met**
6	Check registration status of all drugs included in the shorter regimen	**Not met**
7	Regular and complete monitoring of all patients on second line drugs – ECG and TSH testing should be undertaken as per guidelines – Audiometry equipment need to be purchased at the earliest	**Not met**

b) Current status of country PMDT implementation:

PMDT services are implemented since 2008 through support from GF and technical assistance through WCO TL. Till date, MDR-TB detection and treatment initiation has been provided in all 13 municipalities with diagnosis using 4 GeneXpert® machines and treatment through the Klibur Domin DR-TB treatment center. Additionally, 2 more GeneXpert® machines are procured by NTP. These are proposed to be installed at the Ainaro and Baucau municipalities, for linking these far-off districts to GeneXpert® machines.

TB case detection is a challenge due to passive health seeking behavior of people of TL and poor quality specimen collection and transportation to smear microscopy centers. These are the main reason for low case detection in TB (57% in 2016 and 54% in 2017).

PMDT is integrated with the NTP. The current criteria for presumptive MDR patients include: All smear positive new and retreatment cases; sputum positive at the end of intensive phase and mid-continuation phase, contacts of MDR-TB and TB-HIV. The technicians from the smear microscopy centers collect specimen as per the criteria and transport them to test mainly on the 4 GeneXpert®. GeneXpert® machines have been sub-optimally utilized due to challenges with identification of presumptive TB/DR-TB and specimen collection and transport.

All lab-confirmed RR-TB patients are hospitalized at the Klibur Domin DR-TB center for the complete duration of intensive phase of treatment. Patients are provided MDR-TB treatment free of cost, follow up cultures, nutritional support, adverse drug reaction management and counseling under NTP TL as vertical services. aDSM is limited by lack of lab investigations, equipment and clinical capacity. Specialist and emergency consultations are arranged through national hospital in Dili. Second line drug (SLD) courses are earmarked for every patient initiated on treatment and there are adequate quantities of SLDs available in the country. There are plans to decentralize DR-TB treatment centers to the national and regional referral hospitals in the near future; however, the modalities of decentralization have yet to be clearly defined and operationalized.

In 2017, only 366 (10.5%) of the 3579 notified TB patients were tested for RR-TB and only 4 lab confirmed RR-TB patients were initiated on standard MDR-TB treatment of 20 month duration[1]. This amounts to treatment coverage of only 3% of 130 estimated MDR/RR-TB among notified TB patients (3579) and 1.5% of 260 estimated incident MDR-TB patients as compared to 54% treatment coverage of 6500 incident drug sensitive TB patients estimated in TL. However, the treatment success in the 2015 annual cohort of 4 MDR-TB patients has been reported at 50%. In 2018, only 4 MDR-TB patients have been initiated on treatment so far. Further, 83% TB patients are reported to be facing catastrophic total costs due to TB in 2017.

c) Key challenges identified in this mission (by priority):

The key challenges identified in the current mission are enlisted below:

- Although there is a political commitment expressed for ending TB by 2030 in the National Strategic Plan 2018-22, the enhancement in domestic funding & inter-sectoral/inter-ministerial collaboration for policy refinements, implementing and intensive monitoring of a comprehensive strategy to end TB as enshrined in the national strategic plan. Key known drivers of TB epidemic in TL (malnutrition, smoking, diabetes) unaddressed systematically.

[1] Regimen used for MDR-TB is Intensive Phase : 8 Cm-Eto-Lfx-Cs-Z and Continuation Phase : 12 Eto-Lfx-Cs-Z.

- National technical and operational guidelines for TB & PMDT need to be updated and aligned with the national strategic plan 2018-22, End TB Strategy and the recent WHO guidelines for TB prevention, systematic screening, diagnosis, treatment of TB and MDR/RR-TB, social support and co-morbidity management particularly malnutrition, smoking and diabetes mellitus etc.
- WHO TL and other partners may need to assess and if needed enhance their organizational capacity to meet the technical assistance demands to support GoTL to end TB within the committed time-frame.
- Epidemiology of M/XDR TB is unknown (rates of neighboring countries applied to TL) due to delays in conduct of the national DRS.
- Reaching the unreached - Health seeking behavior of the people has huge barriers to accessing health care services in Timor-Leste that is leading to delays and underutilization of TB services. National programme on comprehensive primary health care services "Saude na familia" initiated in 2015 offers the most suited vehicle to leverage upon for reaching the unreached TB patients in the country.
- The current low sensitivity diagnostic tools[2] and algorithms; variable passive and differential active case finding strategies; poor quality specimen (predominantly saliva) tested on GeneXpert® from presumptive TB that takes precedence over testing presumptive DR-TB are factors that collectively contribute to lower than expected yield of TB and RR-TB.
- National TB reference laboratory has no culture media (LJ media) available since February 18. is not yet proficient in solid or liquid culture DST through SNRL Chennai, the key position of microbiologist is vacant and the DRS protocol needs refinement particularly in transporting culture isolates instead of specimen to ensure good culture recovery at SNRL Chennai. SL-DST capacity is lacking in the country, the culture recovery rate on specimen transported from NTRL Dili for SL-DST to SNRL Chennai was only 29% (11/38) and the mean time for specimen receipt by SNRL Chennai is 30 days.
- MDR-TB treatment services centralized to only one center at Klibur Domin leading to delays in access to care with a strategy of long term hospitalization. The treatment regimen for drug sensitive and drug resistant TB need to be aligned with the recent WHO recommendations. National regulatory approvals have yet to be obtained for some of the WHO recommended second line drugs as per the rapid communication like Mfx, Lzd, Cfz, Bdq, Dlm.
- Treatment adherence monitoring is based on sub-optimally implementation of directly observed treatment with human interface. A paper based TB/DR-TB surveillance system with aggregated reporting is in place except QuanTB for drug logistic management. E/m health solutions not explored in spite of improving

[2] Sputum smear microscopy has a low sensitivity of 66% compared to GeneXpert® of 93.8% compared with Gold Standard of 100% with Culture (Cepheid GeneXpert® MTB/RIF data sheet)

penetration of mobile, social media and internet in the country as well as health information systems under development to serve epidemiological intelligence to the programme for policy refinements in future.

- Atauro Island off Dili identified as the initial site to be made TB Free, however, no clear strategy including latent TB infection (LTBI) available to this effect.

d) Conclusion: priority recommendations:

The top 10 priority recommendations from the current mission are as follows:

SN	Recommendations (preferably not more than 10)	Responsible agency	Time frame
1	***Execute political commitment:*** *Translate high political commitment into enhanced domestic funding & inter-sectoral/inter-ministerial collaboration to address key drivers of TB epidemic like malnutrition, smoking, silicosis, poverty etc. with intensive monitoring of a comprehensive strategy to end TB. Use the opportunity of UN HLM in September 2018 and equivalent forums to reiterate the political commitment to end TB in TL.*	*MoH, NTP supported by WHO-TL and partners*	*Sep 2019*
2	***Update national TB policy and guidelines as per the mapping (Annexure 3):*** *Complete the first draft of updated national guidelines on TB and PMDT guidelines for TL (integrated) within next 90 days and share with WHO SEARO and the author for inputs and finalization within 2018. Conduct a national consultative workshop to deliberate and finalize the guidelines.*	*NTP supported by WHO-TL*	*Dec 2018*
3	***Enhance investments in Technical Assistance:*** *WHO TL and other partners to assess and if needed enhance their organizational capacity to meet the technical assistance demands to support GoTL to end TB within the committed time-frame.*	*WHO-TL and other partners based on request from NTP*	*Dec 2018*
4	***Know your DR-TB epidemic:*** *Expedite initiation of the national DRS after incorporating the recommended refinements detailed in the report in consultation with all stakeholders.*	*NTP supported by WHO-TL*	*Dec 2018*
5	***Reach the unreached:*** *Address the barriers to accessing health care services in Timor-Leste by introducing a comprehensive TB care package with Saude na familia (comprehensive primary health care) with investment in capacity building, motivating the field staff, good quality specimen collection and transport system or more machines (Edge/4module) to cover all municipalities.*	*NTP supported by WHO-TL*	*Dec 2018*

6	***Improve case finding and diagnostics:*** *Develop a standard active case finding strategy for the country with infection control through cough clinics at all levels of health facilities and at community level (SnF, SISCa & NGOs), expand ACF to all municipalities and more vulnerable groups, improve quality of specimen through training, update the diagnostic algorithm for TB & DR-TB with apt positioning of available high sensitivity diagnostic tools and explore WHO endorsed TB lamp (microscopy replacement technology) through support of JICA.*	*NTP supported by WHO-TL and JICA*	*Dec 2018*
7	***Strengthen National TB reference laboratory:*** *Expedite procurement of solid culture media, proficiency testing of NTRL in solid or liquid culture DST through SNRL Chennai for first & second line drugs, position the microbiologist, refine the protocol for specimen transport foo DRS as well as SL-DST to ensure good culture recovery at SNRL Chennai and consider investment in LPA capacity.*	*NTP supported by WHO-TL and KOICA*	*Mar 2019*
8	***Enhance MDR-TB treatment services:*** *Decentralize MDR-TB treatment services with aDSM systems through network of National, regional and municipality level DR-TB centers corresponding to diagnostic services, align treatment regimen with the recent WHO recommendations, expedite approvals of national regulatory authorities for some of the WHO recommended second line drugs as per the rapid communication like Mfx, Lzd, Cfz, Bdq, Dlm.*	*NTP supported by WHO-TL*	*Jun 2019*
9	***Digitalize TB for elimination in TL:*** *Harness the penetration of mobile, social media and internet in TL and invest in electronic case based patient tracking and data management system under HMIS to cover e/m health solutions in the whole spectrum of services from health education to test request to results to treatment to adherence monitoring to aDSM to logistic management to e-records and artificial intelligence (AI) for predictive analysis and prompting course correction in the fight to end TB in TL.*	*NTP supported by WHO-TL*	*Jun 2019*
10	***Switch to end TB mode:*** *Develop a clear comprehensive strategy (prevent, test, treat, rehabilitate) for TB Free Atauro Island off Dili including LTBI and document the initial learnings for refinement and scale up across TL.*	*NTP supported by WHO-TL*	*Jun 2019*

The NTP officials agreed to all of the above recommendations with support of Dr S Anand that was discussed at the debriefing meeting on 31 August 2018. For the revision of the guidelines the following course of action was agreed upon:

- Mapping of the updates in the national guidelines developed in consultation with NTP, TB experts, WHO officials was agreed as the outline to move ahead
- WHO TA will continue the support to NTP in developing the first draft of the guidelines.
- NTP to share the first draft with WHO SEARO and the author for further inputs and finalization
- National consultative workshop to be organized with the national experts once the first draft is ready.

The recommendations were gracefully accepted by the key officials of NTP, and WHO as the author exercised transparency and openness to suggestions from them to enable refinement, improvisation and ownership for enactment.

The NTP and WHO TL also requested the author to continue providing inputs after the mission to finalize the national TB guidelines with drug resistant TB as an integral part of the strategy.

II. Detailed report:

A. Introduction/Background

Timor-Leste is an island nation with a population of 1.3 million and an annual population growth rate of 1.8%. The country has made substantial progress in re-establishing infrastructure after massive destruction in 1999 and 2006. The country remains one of the least developed nations in Asia, ranking at 133 out of 188 countries on the Human Development Index (2015). Approximately 31.1% of the population lives below the national poverty line, living on less than US$ 0.88 per person per day. Life expectancy at birth was 68.2 years in 2014. A large part of country consists of difficult terrain. The hilly and mountainous areas make travel difficult and because of scattered population, there are large distances between residence and microscopy centers.

Public Health Expenditure was 1.3% of total GDP in 2014. Additionally, the Ministry of Health (MoH) receives financial and technical assistance for various health priority programmes through bilateral aid, multilateral agencies, UN agencies, the Global Fund and others.

B. Existing TB control program

TB Burden:

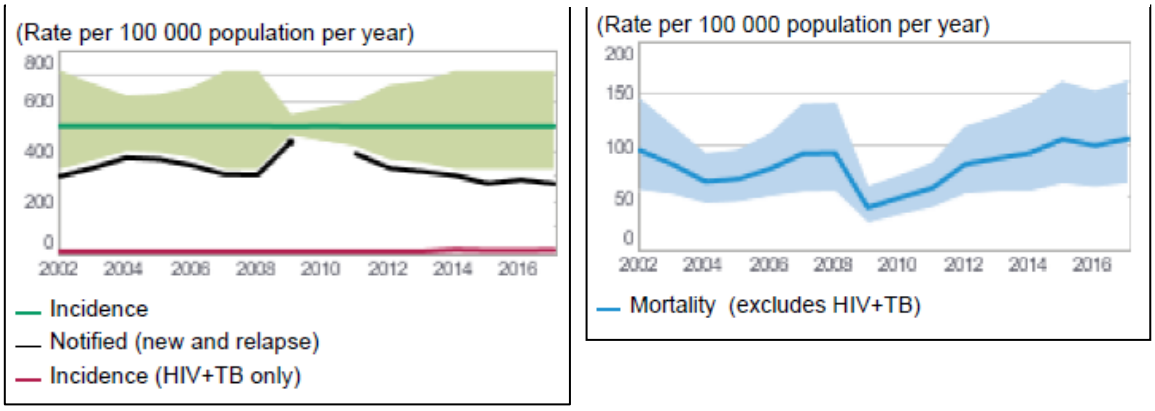
Democratic Republic of Timor-Leste is one of the high tuberculosis (TB) burden countries in the South-East Asia Region. Current estimates indicate that TB prevalence and mortality from TB in the country are among the highest in the South-East Asia region after DPR Korea.

The TB burden and draft profile of TL submitted for the Global TB Report 2018 is annexed with this report. The epidemiological analysis reported in external review mission report of 2017 was also referred to. WHO estimates are based on regional data as a prevalence survey has not been conducted in TL. The salient observations are as follows:

- In 2017, TB incidence is estimated at 498/100,000 population in TL (Figure 1). However, notification rate per 100,000 populations of all forms of newly notified TB case has declined continuously over the period of 2010-2017 with geographical heterogeneity between municipalities. With this declining trend and 3579 TB patients notified in 2017 (275/100,000), TL has achieved only 54% treatment coverage of 6500 estimated incident TB patients (498/100,000), leaving a huge treatment gap of ~46%. This translates to 2921 TB patients missing from TB notification and treatment in 2017.

- In 2017, TB killed 106 people per 100,000 people (1400 per annum) in TL with an increasing mortality trend (Figure 1), in spite of TB services being available since nearly two decades.

Figure 1: Trends of TB Incidence, notification and mortality in TL



- Malnutrition and smoking are the top two known drivers of the TB epidemic synergizing with TB menace to kill people in TL calling for urgent attention.
- In 2017, 83% TB patients are reported to be facing catastrophic total costs due to TB in 2017.
- Sustaining engagement of private sector, active case finding for TB, regulated supply of quality assured anti-TB drugs through NTP, regular practice of infection control, protection of contacts and sustained high treatment success rates are factors that could prevent emergence and spread of drug-resistance.

NTP & its structure:

TB services are a part of the comprehensive service package and delivered through a network of facilities in the healthcare delivery system. Dili has the National Hospital known as Hospital Nacional Guido Valadares (HNGV) is the largest referral and tertiary care set up in TL. For secondary health services, there are 5 referral hospital located in the municipalities of TL namely, Baucau, Bobonaro, Covalima, Oecusse and Ainaro. The public health care delivery facilities in the 13 Municipality of Timor-Leste include 66 community health centers (CHCs), 321 health posts, 162 mobile clinics (all providing primary health care to the community), and linking with six referral hospitals providing mainly secondary and tertiary care. Under the Servisu Integradu da Saúde Communitária (SISCa) initiative over 470 SISCa health posts are being established for health out-reach activities. The facilities are currently resourced by about 2500 Timorese health workers with the support of around 10-12 specialists consultants appointed by Royal Australian College of Surgery (RACS) and a Cuban Brigade with many specialist doctors and health workers. The health staffs in TL are trained in Cuba, Indonesia, Fiji, Malaysia or Australia

As part of the GoTL's constitutional commitment to rebuild the health infrastructure destroyed in 1999 and to fulfil rights to free universal health care of its people through a decentralized public health care system, **"Programa Nasional Saude na Familia"** based on Cuban model was launched in 2015 as a comprehensive service package of primary health care to the household level through domiciliary visits by a team of a doctor, a midwife and a nurse; clinical consultations; treatment and referral by team of health professionals; as well as recording the household's and each of its member's clinical profiles, which are then being entered into an integrated digitalized medical record system. This aligns with the spirit of Sustainable Development Goals of "leaving no one behind". It covers all the 296,483 households and 2,225 villages (Sukos) mapped in the census of 2015.

The Central Management Unit of Tuberculosis (CMU-TB) under the Communicable Diseases Control (CDC) Department under MoH, headed by NTP manager, is responsible for formulation of technical and operational guidelines and policies, planning and overall implementation of programme activities in the country including coordination, monitoring and evaluation. Currently the Central TB Unit is staffed by a Programme Officer, five regional supervisors (RS), one finance officer, and one monitoring and evaluation (M&E) officer, a data entry assistant, one training officer and an administrative assistant.

The Municipality TB coordinator (DTC), based at the Municipality health services (DHS) is specifically responsible for the organization of TB activities and for overseeing the implementation of TB program in the Municipality. The mainstay of diagnosis is sputum microscopy. There are 75 TB laboratories including 66 in CHCs and 9 in private clinics. There are 4 GeneXpert® machines located at the National Tuberculosis Reference Laboratory (NTRL), Klibur Domin, Bairo Pite Clinic and a referral hospital. Additionally, 2 more GeneXpert® machines are procured by NTP. These are proposed to be installed at the Ainaro and Baucau municipalities, for linking these far off districts to GeneXpert® machines. The NTRL has a BSL 3 culture and DST laboratory developed by KOICA and functioning since April 2016. The doctors and health personnel at the health post and CHC level are responsible for patient referral and sputum transportation.

While the health infrastructure and workforce is mainly contributed by the GoTL, the global fund supports equipment, lab consumables, drugs, trainings, and technical assistance through partners.

C. Information on M/XDR-TB

Epidemiology of M/XDR TB is largely unknown except for prevalence of MDR-TB. Applying the regional prevalence estimates of Kupang of Indonesia, MDR-TB is estimated to be 3.3% in new and 18% in previously treated patients, while the proportion with XDR-TB is unknown. This extrapolates to an estimate of an incident 260 (20/100,000) MDR-TB emerging in TL annually. Further, a national drug resistance survey is expected to commence in 2018 to measure the burden of M/XDR-TB. A series of national trainings of key staff and technicians of TL as well as the national reference laboratory staff was conducted, and the national DRS protocol reviewed in consultation with the supra-national reference laboratory at Chennai.
The country initiated PMDT services with external support of The Global Fund (GF) since 2008 and technical assistance from WHO Country Office-TL. PMDT services are available across all municipalities of the country under the NTP framework and are currently supported by commodity cum technical support by GF-NFM funding. Other partner organizations like Caritas Dili (Catholic Institution), Klibur Domin (NGO), Bairo Pite Clinic (NGO), International Organization of Migration (IOM), Burnet Institute (Donor and Implementing partner), Café Cooperativa Timor Clinic (Corporate Sector partner), Korea International Cooperation Agency (KOICA) and Japan International Cooperation Agency (JICA) have also been supporting TL particularly in active case finding, nutrition support, laboratory expansion, private sector engagement and treatment of TB and DR-TB.

Till date, MDR-TB detection and treatment initiation has been provided in all 13 municipalities with diagnosis using 4 GeneXpert® machines and treatment through the Klibur Domin DR-TB treatment center. TB case detection is a challenge due to passive health seeking behavior of people of TL and poor quality specimen collection and transportation to smear microscopy centers.

PMDT was initiated in the country since 2008 and is integrated with the NTP. The current criteria for presumptive MDR patients includes: All smear positive new and retreatment cases; sputum positive at the end of intensive phase and mid-continuation phase, contacts of MDR-TB and TB-HIV. The technicians from the smear microscopy centers collect specimen as per the criteria and transport them to test mainly on the 4 GeneXpert®. GeneXpert® machines have been sub-optimally utilized due to challenges with identification of presumptive TB/DR-TB and specimen collection and transport.

All lab-confirmed RR-TB patients are hospitalized at the Klibur Domin DR-TB center for the complete duration of intensive phase of treatment. Patients are provided MDR-TB treatment free of cost, follow up cultures, nutritional support, adverse drug

reaction management and counseling under NTP TL as vertical services. aDSM is limited by lack of lab investigations, equipment and clinical capacity. Specialist and emergency consultation is arranged through national hospital in Dili. Second line drug (SLD) courses are earmarked for every patient initiated on treatment and there are adequate quantities of SLDs available in the country. There are plans to decentralize DR-TB treatment centers to the national and regional referral hospitals in the near future; however, the modalities of decentralization have yet to be clearly defined and operationalized.

In 2017, only 366 (10.5%) of the 3579 notified TB patients were tested for RR-TB and only 4 lab confirmed RR-TB patients were initiated on standard MDR-TB treatment of 20 month duration. This amounts to treatment coverage of only 3% of 130 estimated MDR/RR-TB among notified TB patients (3579) and 1.5% of 260 estimated incident MDR-TB patients as compared to 54% treatment coverage of 6500 incident drug sensitive TB patients estimated in TL. However, the treatment success in the 2015 annual cohort of 4 MDR-TB patients has been reported at 50%. In 2018, only 4 MDR-TB patients have been initiated on treatment so far. Further, 83% TB patients are reported to be facing catastrophic total costs due to TB in 2017.

Key Observations:

- Epidemiology of M/XDR TB is unknown (rates of neighboring countries applied to TL) due to delays in conduct of the national DRS. Since, rifampicin was introduced in TL very recently (2015), the population exposure to this drug and the resulting acquired resistance to rifampicin is expected to be lower than the neighbors.

- The following key observations were made during the review of the national DRS protocol for further refinements (Annexure 5):
  a) The remnant portion of specimen collected for microscopy to be stored in the refrigerator, transported to the district where they are packaged and stored for dispatch on scheduled days a week to the National Laboratory.
  b) Specimens are to be collected in sputum cups, packaged and transported.
  c) The secondary container in the triple layer packaging does not indicate absorbent material.
  d) GeneXpert® will be performed on one of the specimens. The other specimen will be aliquoted, and one aliquot processed for culture and the other sent to SNRL – NIRT, Chennai, India for Culture and DST.
  e) Certain consumables and accessory laboratory are not available for the laboratory procedures.

Recommendations:

1. *Know your DR-TB epidemic:*

Expedite initiation of the national DRS after incorporating the recommended refinements detailed in the report in consultation with all stakeholders.

Responsibility: NTP with support of WHO TL
Timelines: December 2018

2. *Refine the national DRS protocol:*

The following refinements are recommended for consideration of NTP after obtaining consensus from all stakeholders:

f) Two additional specimens (C & D) to be collected for the DRS from the smear positive patients and dispatched soon after collection directly to the National laboratory.
g) Collect specimen in Falcon tubes, pack and transport.
h) A layer of absorbent cotton to be placed around the tubes as per the guidelines for specimen transport.
i) National laboratory will decontaminate the both the specimens (NALC NaoH). The decontaminated sediments will be used for preparing smear and for inoculating Culture tubes.
  i) 0.5 ml of one of the sediments will be used for performing GeneXpert® test.
  ii) The growth obtained on Culture will be confirmed as M. tb using immune-chromatography test (ICT test).
  iii) Glycerol stocks will be prepared of the M. tb isolates, checked for purity and dispatched to NIRT, Chennai for performing DST.
j) The consumables and accessories will have to be procured and used.

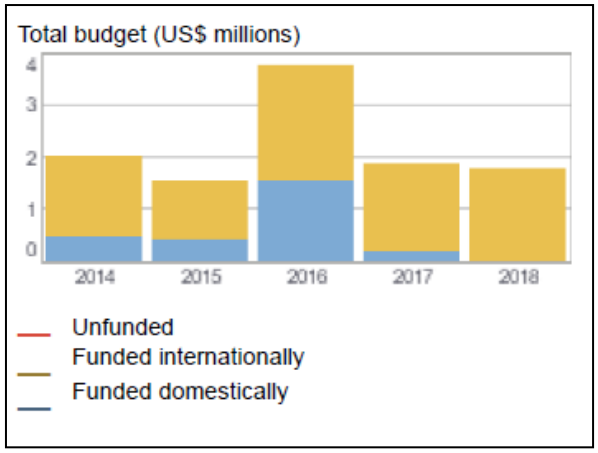
Responsibility: NTP with support of WHO TL
Timelines: December 2018

D. Government commitment

The MoH and NTP are committed to implementation of Programmatic Management of Drug Resistant TB (PMDT) and incorporating the WHO recommendations towards ending TB. This commitment translates into an ambitious national strategic plan 2018-21 that aims for universal DST by 2021.

In 2017, of the total national TB budget of around 1.8 million USD, the domestic funding continues to decline since 2016 (Figure 2). However, it was learnt during interaction with stakeholders that the government acts humble in completely reporting the expenditures particularly in infrastructure, human resources etc. and hence, it's giving a picture of almost complete dependence on international funding. If this is considered, in 2018, the total national TB budget is ~ 3.5 million; of which domestic budget is ~ 1.6 million. GoTL is committed to increase the domestic funds during GF NFM Phase II funding request (2018-2021) to address the funding gap.

Figure 2: TB Financing - 2018



The major areas of funding gap identified include enhancements in diagnostic capacity (lab equipment, consumables, training, sample transport); treatment capacity (decentralized IC compliant DR-TB treatment centers with aDSM capacity, uninterrupted supply of adequate quantities of quality assured second line drugs); ICT interventions (for surveillance and adherence monitoring); patient support and enablers (social protection, nutrition, adherence support, travel support) etc. The government is committed in investment towards building capacity of infrastructure, human resource development and social protection to eliminate catastrophic expenditures etc.

Key Observations:

- Although there is a political commitment expressed for ending TB by 2030 in the National Strategic Plan 2018-22, enhancement is needed in domestic funding & inter-sectoral/inter-ministerial collaboration for policy refinements, implementing and intensively monitoring of a comprehensive strategy to end TB as enshrined in the national strategic plan. Key known drivers of TB epidemic in TL (malnutrition, smoking, diabetes) are not addressed systematically.

- Further, the national technical and operational guidelines for TB & PMDT need to be updated and aligned with the national strategic plan 2018-22, End TB Strategy and the recent WHO guidelines for TB prevention, systematic screening, diagnosis, treatment of TB and MDR/RR-TB, social support and co-morbidity management particularly malnutrition, smoking and diabetes mellitus etc. During the mission, mapping of the updates required in the national guidelines was done in consultation with the NTP manager, his team, national experts and WHO TL to guide further refinement of the guidelines (Annexure 3)

Recommendations:

1. ***Execute political commitment:***

   Translate high political commitment into enhanced domestic funding & inter-sectoral/inter-ministerial collaboration to address key drivers of TB epidemic like malnutrition, smoking, silicosis, poverty etc. with intensive monitoring of a comprehensive strategy to end TB. Use the opportunity of UN HLM in September 2018 and equivalent forums to reiterate the political commitment to end TB in TL.

   Responsibility: MoH, NTP supported by WHO-TL and partners
   Timelines: September 2019

2. ***Update national TB policy and guidelines as per the mapping (Annexure 3):***

   Complete the first draft of updated national guidelines on TB and PMDT guidelines for TL (integrated) within next 90 days and share with WHO SEARO and the author for inputs and finalization within 2018. Conduct a national consultative workshop to deliberate and finalize the guidelines.

   Responsibility: NTP with support of WHO TL
   Timelines: December 2018

E. Partnerships within GoTL and with private sector

The major technical support for the NTP is provided by World Health Organization. NTP has also received technical and commodity assistance from Global Drug Facility (GDF), UNITAID, Green light Committee (GLC), NIRT Chennai, and independent consultants.

The country initiated PMDT services with external support of The Global Fund (GF) since 2008 and technical assistance from WHO Country Office. PMDT services are available across all municipalities of the country under the NTP framework and are currently supported by commodity cum technical support by GF-NFM funding. Other partner organizations like Caritas Dili (Catholic Institution), Klibur Domin (NGO), Bairo Pite Clinic (NGO), International Organization of Migration (IOM), Burnet Institute (Donor and Implementing partner), Cooperativa Café Timor (CCT) Clinic (Corporate Sector partner), Korea International Cooperation Agency (KOICA) and Japan International Cooperation Agency (JICA) have also been supporting TL particularly in active case finding, nutrition support, laboratory expansion, private sector engagement and treatment of TB and DR-TB.

The general health system under the MoH is the primary providers of services for TB and DR-TB in TL. In Timor-Leste, TB medications by legislation are not sold in any private pharmacy or available in any private/faith based or NGO clinics. However, smear microscopy facilities are available in 9 private clinics across TL. It was informed that all TB patients seeking care in private clinics are notified to NTP for provision of anti-TB drugs.

Key Observations:

- The NTP has initiated engagement with private practitioners and this has resulted in the recent referrals, but no formal "Public- Private Mix" or "TB Notification" policy has been developed.

- WHO TL and other partners may need to assess and if needed enhance their organizational capacity to meet the technical assistance demands to support GoTL to end TB within the committed time-frame.

Recommendations:

1. ***Formalize "Partnership" or "TB Notification" policy:***

   NTP, GoTL to formalize a national policy to promote partnership with private providers or to ensure notification of TB and DR-TB patients with clear public health actions to extend services to TB patients seeking care in the private sector as well as a mutually acceptable accountability framework.

   Responsibility: NTP with support from WHO TL and other partners
   Timelines: March 2019

2. ***Enhance investments in Technical Assistance:***

   WHO TL and other partners need to assess and if needed, enhance their organizational capacity to meet the technical assistance demands to support GoTL to end TB within the committed time-frame.

   Responsibility: WHO-TL and other partners based on request from NTP
   Timelines: December 2018

F. Case finding strategy

"I go I die, I stay, I die, better to stay and die in my house"[3]: understanding the barriers to accessing health care in Timor-Leste, a recent publication, revealed lack of transportation; heavy transportation cost; sub-optimal standards of care and hygiene in hospitals; and preference to consider traditional medicine providers as affordable, accessible and acceptable as the main barriers to accessing health care in TL. The solutions recommended in the publication include improving availability of functional transport services; offering travel subsidies or enablers; training health staff to improve standards of professional care; and improving access to quality primary health care. These apply to TB services as well and the right platform for integration of TB services with quality primary health care is now available through Saude na familia.

Currently, the following case finding strategies are implemented in TL:

1. Passive case finding for TB and DR-TB:
   - Presumptive TB patients are identified by the staff at the health post or CHC and referred for sputum smear microscopy at the nearest of the 76 DMC.
   - The technicians from the smear microscopy centers collect specimen from all smear positive TB patients and the high risk presumptive MDR-TB patients i.e. failures of first line treatment or contacts of MDR-TB patients and transport them to test mainly on the 4 GeneXpert®.
   - Specimen collection and transport is incentivized but is weakly implemented and constrained due to geography or lack of transport services.
2. Active case finding for TB:
   - Under the current global fund grant, contractual staffs of Klibur Domin, IOM and Caritas NGOs are conducting active case finding activities for TB in high risk settings like prisons, army, orphans, contacts, diabetes and PLHIV in identified 33 sub-district units in 9 municipalities of TL. All three NGOs are using different strategies for active case finding. One project uses X-Ray and then sputum sample sent for Xpert® MTB/RIF; another project send the sputum for microscopy and third uses only Xpert® MTB/RIF.

Notification rate per 100,000 populations of all forms of newly notified TB case has declined continuously over the period of 2010-2017 with geographical heterogeneity between municipalities. With this declining trend and 3579 TB patients notified in 2017 (275/100,000), TL has achieved only 54% treatment coverage of 6500 estimated incident TB patients (498/100,000), leaving a huge treatment gap of ~46%. This

[3] Price JA, Soares AIFS, Asante AD et al. I go I die, I stay, I die, better to stay and die in my house": understanding the barriers to accessing health care in Timor-Leste. *BMC Health Services Research* (2016) 16:535 DOI 10.1186/s12913-016-1762-2

translates to 2921 TB patients missing from TB notification and treatment in 2017. In 2017, only 366 (10.5%) of the 3579 notified TB patients were tested for RR-TB.

Further, it was learnt that NTP is in discussion with JICA on introducing the new WHO endorsed rapid molecular test for TB diagnosis "TB Lamp" at two sites as a smear microscopy replacement technology for a pilot implementation.

Key Observations:

- Reaching the unreached - Health seeking behavior of the people has huge barriers to accessing health care services in Timor-Leste that is leading to delays and underutilization of TB services. National programme on comprehensive primary health care services "Saude na familia" initiated in 2015 offers the most suited vehicle to leverage upon for reaching the unreached TB patients in the country.

- The current low sensitivity diagnostic tools and algorithms; variable passive and differential active case finding strategies; poor quality specimen (predominantly saliva) tested on GeneXpert® from presumptive TB that takes precedence over testing presumptive DR-TB are factors that collectively contribute to lower than expected yield of TB and RR-TB.

Recommendations:

1. ***Reach the unreached:***

   Address the barriers to accessing health care services in Timor-Leste by introducing a comprehensive TB care package with Saude na familia (comprehensive primary health care) with investment in capacity building, motivating the field staff, good quality specimen collection and transport system or more machines (Edge/4module) to cover all municipalities.

   Responsibility: NTP supported by WHO-TL
   Timelines: December 2018

2. ***Improve case finding and diagnostics:***

   Develop a standard active case finding strategy for the country with infection control through cough clinics at all levels of health facilities (Annexure 4) and at community level (SnF, SISCa & NGOs), expand ACF to all municipalities and more vulnerable groups, improve quality of specimen through training, update the diagnostic

algorithm for TB & DR-TB with apt positioning of available high sensitivity diagnostic tools (Annexure 4) and explore WHO endorsed TB lamp (microscopy replacement technology) through support of JICA.

Responsibility: NTP supported by WHO-TL and JICA
Timelines: December 2018

G. Laboratory services

The mainstay of TB diagnosis is sputum smear microscopy. There are 75 TB laboratories including 66 in CHCs and 9 in private clinics. There are 4 GeneXpert® machines located at the National Tuberculosis Reference Laboratory (NTRL), Klibur Domin, Bairo Pite Clinic and a referral hospital at Bobonaro. NTP has also procured 2 GeneXpert® machines and intends to install it at the Ainaro and Baucau municipalities for linking these far off districts to GeneXpert®. The NTRL has a BSL 3 culture and DST laboratory developed by KOICA and functioning since April 2016. The laboratory was performing solid culture and DST using the Ogawa method for the first line drugs of Isoniazid, Rifampicin, Streptomycin and Ethambutol and in addition to 2 key second line drugs Ofloxacin and Kanamycin on limited samples till February 2018. Proficiency testing for first line DST on solid culture has not yet initiated through SNRL. One MGIT 360 machine is expected to be supplied through the Global Fund by September 2018. There is no LPA facility available in the NTRL, however, there is adequate PCR capacity and space available in the national hospital lab where NTRL is co-located.

Quality assurance for smear microscopy centers are provided by NTRL, regional and municipality level TB coordinators through on-site supervision and external quality assurance. The quality of microscopy and the mechanism of quality assurance for smear microscopy were verified during visit to the microscopy centers at Klibur Domin and NTRL. Bacteriological confirmation and follow up of drug sensitive TB is primarily based on smear microscopy across TL.

DR-TB diagnostic services are primarily based on GeneXpert® while it was informed that fresh specimen from the RR-TB patients detected are collected and transported for second line DST to SNRL Chennai. Under the NSP 2018-22 & GF NFM Phase II, laboratory expansion has been proposed with additional GeneXpert® machines and an LPA for NRTL to meet the diagnostic demands of TL for universal DST.

Key Observations:

- National TB reference laboratory has no culture media (LJ media) available since February 18. is not yet proficient in solid or liquid culture DST through SNRL Chennai, the key position of microbiologist is vacant and the DRS protocol needs

refinement particularly in transporting culture isolates instead of specimen to ensure good culture recovery at SNRL Chennai. SL-DST capacity is lacking in the country, the culture recovery rate on specimen transported from NTRL Dili for SL-DST to SNRL Chennai was only 29% (11/38) and the mean time for specimen receipt by SNRL Chennai is 30 days.

- Requirements for LPA and the quantum of additional GeneXpert® machines and cartridges required in the NSP period would change with the revision of the diagnostic algorithm and expansion of active case finding strategies detailed above.

- Only one of the five technicians was formally trained in culture and DST technique at Japan. There is a larger team of ~40 technicians in the laboratory of the national hospital with varied skillsets including conducting PCR.

- There exists no formal mechanism to sustain the annual maintenance of the laboratory equipment's and air handling unit of BSL III laboratory developed by KOICA, nor is there an in house bio-medical technician to address maintenance needs in the laboratory.

Recommendations:

1. ***Strengthen National TB reference laboratory:***

   Expedite procurement of solid culture media, proficiency testing of NTRL in solid or liquid culture DST through SNRL Chennai for first & second line drugs, position the microbiologist, refine the protocol for specimen transport foo DRS as well as SL-DST to ensure good culture recovery at SNRL Chennai and consider investment in LPA capacity.

   Responsibility: NTP supported by WHO-TL and KOICA
   Timelines: March 19

2. ***Procure LPA and additional GeneXpert® machines :***

   Expedite procurement of LPA and simultaneous quantification of additional GeneXpert® machines and cartridges to meet the annual demand forecasted based on the revision of the diagnostic algorithm and expansion of active case finding strategies as well as to cover at least all municipalities.

   Responsibility: NTP supported by WHO-TL
   Timelines: March 19

3. ***Strengthen human resource capacity of NTRL:***

In consultation with the head of laboratory at national hospital, identify technicians from the larger team of ~40 technicians with basic training and skillsets in conducting culture, DST, PCR (for LPA) and formally trained internationally to form the core team of technicians to conduct the highly skilled function at NTRL. Further, consider formal international training of at least 5-7 additional staff from NTRL.

Responsibility: NTP, National Hospital Laboratory supported by WHO-TL
Timelines: December 18

4. ***Establish sustainable maintenance mechanism for NTRL:***

In consultation with the head of laboratory at national hospital, establish a sustainable annual maintenance contract as well as hire a qualified bio-medical engineer to ensure regular safety and maintenance of the equipments and air handling unit (BSL III).

Responsibility: NTP, National Hospital Laboratory supported by WHO-TL and KOICA
Timelines: December 18

A detailed report on Laboratory assessment and National DRS trainings conducted by Dr S Anand, WHO RNTCP National Consultant TB Laboratories, New Delhi with the author alongside the mission is available for reference at Annexure 5.

H. Treatment strategy

Treatment for drug sensitive TB is initiated by the doctors at the CHC in all 13 municipalities using standard first line regimen CAT I (2HREZ/4HR) and CAT II (2HREZS/1HREZ/5HR) for new and previously treated patients respectively.

Treatment for MDR/RR-TB patients is initiated through the Klibur Domin DR-TB treatment center using standard second line regimen (8 Cm Lfx Eto Cs E Z / 12 Cm Lfx Eto Cs E) in accordance to the WHO PMDT guidelines (2011) after a complete pre-treatment evaluation as per the current guidelines. There is no standard regimen defined for differential treatment of H mono/poly DR-TB and XDR TB patients in TL.

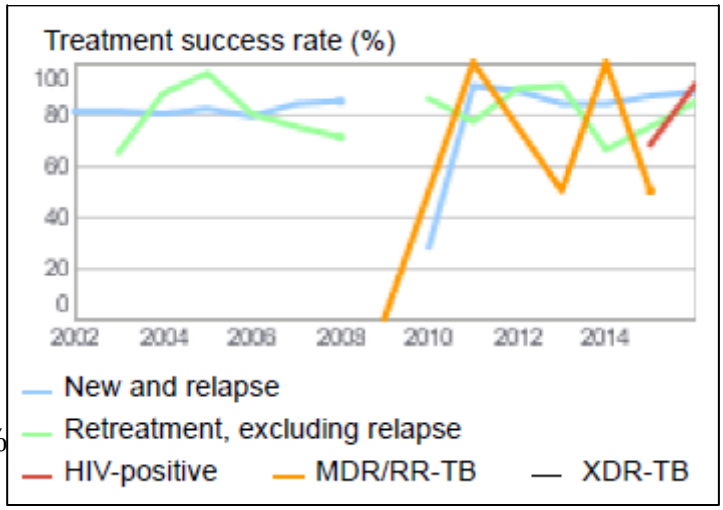
All lab-confirmed RR-TB patients are hospitalized at the 14 bedded infection control compliant wards at the Klibur Domin DR-TB center for the complete duration of intensive phase of treatment. Patients are provided MDR-TB treatment free of cost,

follow up cultures, nutritional support (~150$ per month while admitted), adverse drug reaction management and counseling under NTP TL as vertical services. aDSM is limited by lack of lab investigations, equipment and clinical capacity. Facilities for ECG and audiometry are not routinely available. Serum electrolytes, specialist and emergency consultation are arranged through national hospital in Dili. Surgery is not conducted on TB patients as thoracic surgical facilities are not available in the country. Fortunately, no such complicated TB cases requiring surgical interventions have emerged yet. Second line drug (SLD) courses are earmarked for every patient initiated on treatment and there are adequate quantities of SLDs available in the country. Four MDR-TB patients admitted at the time of visit were interviewed.

The National Hospital was visited where high level of commitment and zeal was expressed by the Director and the specialist to reconstitute the national aDSM committee into a national DR-TB expert committee of clinical multi-specialists including aDSM functions, state of the art infection control compliant services for TB and DR-TB including cough corner and fast-tracking of presumptive TB patients to diagnostic services, a separate ward for TB and DR-TB backed up by all requisite investigations, oxygen, ventilator support, automated ECG, audiometry, cardiologist and other specialist services required for initiating patients on newer drugs like Bedaquiline, capacity building and national referral center for serious patients. The Specialist Pulmonologist met has experience of managing MDR-TB patients in his previous posting at Papua New Guinea. There are plans to decentralize DR-TB treatment centers with a decentralized model of care from national hospital to the regional referral hospitals in the near future; however, the modalities of further decentralization to municipalities have yet to be clearly defined and operationalized.

In 2017, only 4 lab confirmed RR-TB patients as compared to 3579 TB patients, were initiated on standard treatment. This amounts to treatment coverage of only 3% of 130 estimated cases out of notified and 1.5% of 260 incident MDR-TB patients as compared to 54% treatment coverage of 6500 incident drug sensitive TB patients estimated in TL. In 2018, only 4 MDR-TB patients have been initiated on treatment so far. One XDR-TB patient was detected in 2018 that died before initiation of treatment.

Figure 3: Trend of treatment success rates



Treatment success is consistently near to 90% among new TB patients and has improved to 85%

among previously treated TB patients in the past three years. However, it fluctuates between 50-100% in MDR-TB cohorts due to small numbers. In the 2015 annual cohort of 4 MDR-TB patients, 2 were successfully treated (Figure 3). Moreover, with increasing notification of all types of TB patients particularly relapses, the trends of treatment outcomes may decline if ambulatory care and support systems are not strengthened.

The ambulatory treatment services for TB and DR-TB are regular but nutrition support is systematically not extended beyond the admission period. Direct observation of treatment is the mainstay for adherence monitoring; however like diagnostic services; there remain unaddressed challenges with barriers to accessing health care driving the health seeking behavior of people of TL for monitoring progress on treatment, follow up investigations and adverse event management and monitoring. Hence, family members as observers or self-administration of daily doses are resorted to in many patients especially in hard to reach areas.

The mission also covered a deliberation at Dili with NTP manager, regional TB coordinators, specialists from National Hospital and WHO staff with special focus on the WHO Rapid Communication on treatment of MDR/RR-TB to review and discuss around the revision of TL's PMDT guidelines to include options of updated integrated TB and DR-TB diagnostic algorithms complemented by active case finding and infection control in out-patient department through cough corners, inclusion of universal DST through GeneXpert® and second line LPA, injection free MDR-TB regimen with inclusion of newer drugs like Bedaquiline, effective management of adverse drug reactions (ADR) including concepts of active drug safety monitoring and management (aDSM). As the country has not yet introduced shorter MDR-TB regimen, there was a consensus to consider transition from an injectable containing 20 month regimen to an all oral 20 month regimen as per the WHO rapid communication. There was willingness to take up procurement adjustments with GDF and regulatory approval for use of newer and repurposed second line drugs.

Key Observations:

- MDR-TB treatment services centralized to only one center at Klibur Domin leading to delays in access to care with a strategy of long term hospitalization. The treatment regimen for drug sensitive and drug resistant TB need to be aligned with the recent WHO recommendations. National regulatory approvals have yet to be obtained for some of the WHO recommended second line drugs as per the rapid communication like Mfx, Lzd, Cfz, Bdq, Dlm.

- Treatment adherence monitoring is based on sub-optimally implementation of directly observed treatment with human interface.

- Nutritional assessment and supplementation is available only for DR-TB patients (~150$ per month) during their admission period but there exists no system to continue extending this support for drug sensitive and drug resistant TB patients during their ambulatory care. Further, the existing National Nutritional Strategy, KONSANTIL – national committee for food security on nutrition supported by FAO, WFP, UNICEF, USAID have clear policies and strategies for fortification and supplementation for pregnant/lactating women, children with moderate or severe acute malnutrition delivered through health post, SISCa and SnF mechanisms, these strategies and provisions are not extended to the TB patients and their family contacts (most of them being malnourished).

- Although, the national aDSM committee chairperson was identified from the National Hospital based on the previous rGLC mission recommendations, the concerned doctor has moved on. There is a need for a more robust structure to guide national policy decisions on diagnostics, treatment strategies including clinical management and aDSM that can be served by the National hospital.

Recommendations:

1. ***Enhance MDR-TB treatment services:***

   Decentralize MDR-TB treatment services with aDSM systems through network of National, regional and municipality level DR-TB centers corresponding to diagnostic services, align treatment regimen with the recent WHO recommendations (Annexure 6), expedite approvals of national regulatory authorities for some of the WHO recommended second line drugs as per the rapid communication like Mfx, Lzd, Cfz, Bdq, Dlm.

   Responsibility: NTP supported by WHO-TL
   Timelines: June 19

2. ***Enhance treatment adherence monitoring:***

   Strengthen direct observation of treatment through training of family members and SnF staff while simultaneously exploring digital solutions like Video DOT, 99DOTS etc. to complement real-time adherence monitoring.

   Responsibility: NTP supported by WHO-TL
   Timelines: March 19

3. ***Expand nutrition support to all TB patients and their family:***

   Establish an intersectoral collaborative mechanism between MoH and KONSANTIL to extend decentralized services for nutritional assessment and supplementation to TB patients and their family through SnF mechanisms.

   Responsibility: NTP, KONSANTIL supported by WHO-TL, FAO, WFP, UNICEF, USAID
   Timelines: March 19

4. ***Leverage on Stewardship of National Hospital for TB and MDR-TB:***

   Establish a national DR-TB expert committee of clinical multi-specialists including aDSM functions, state of the art infection control compliant services for TB and DR-TB including cough corner and fast-tracking of presumptive TB patients to diagnostic services, a separate ward for TB and DR-TB backed up by all requisite investigations, oxygen, ventilator support, automated ECG, audiometry, cardiologist and other specialist services required for initiating patients on newer drugs like Bedaquiline, capacity building and national referral center for serious patients.

   Responsibility: NTP, National Hospital supported by WHO-TL and partners
   Timelines: March 19

I. Program management and coordination

The MoH coordinates TB and PMDT services irrespective of funding sources through NTP manager, regional coordinators and district TB coordinators. The MoH oversees the whole process and funding for MDR-TB management in the country to avoid any duplication of support from different donors.

Key Observations:

- PMDT services are centralized in all aspects that contributes to system delays and patient inconveniences. With PMDT service expansion in future, decentralization of the above would be necessary for system to cope with the case load. The following PMDT services were observed to be centralized:
  i) Sample collection and transport system
  ii) Drug Susceptibility Testing
  iii) Pre-treatment evaluation
  iv) Institutional management of MDR-TB throughout treatment
  v) Bio-chemical investigation for ADR Monitoring

Recommendations:

1. ***Decentralize PMDT services:***

   Systematically decentralize PMDT services in all aspects that can minimize system delays and patient inconveniences in the diagnostic treatment pathway. Enlist facilities up to which decentralization could be feasibly done for each of the above enlisted service delivery components. Plan for resource mapping, mobilization and capacity building of the concerned facilities where the above services are proposed to be decentralized. Strengthen the supervision and monitoring components from the higher to the immediate next level of service delivery to ensure mentoring, troubleshooting and streamlining of services.

   Responsibility: NTP, National Hospital supported by WHO-TL and partners
   Timelines: March 19

J. Drug management:

First line anti-TB drugs (4FDC) and all second line anti-TB drugs are centrally procured through GDF using the Global Fund grants. There exists no domestic source of funding for drug procurement. Servisu Autonomo Medicamesto Equipmento Saude (SAMES) which is an autonomous agency for procurement of logistics and drugs etc. is responsible for clearance, storage and distribution of TB medicines including SLDs using QaunTB software. The MDR drugs are stored in a temperature controlled room within the larger SAMES drug store at Dili. No stock-outs reported at any of the places visited. Medicines were found to be well stored and organized.

Key Observations:

- Near expiry stocks of Levofloxacin 250 mg with expiry date of September 2018 were observed in stock at the drug store visited at Klibur Domin DR-TB Center.

Recommendations:

1. ***Systematically avert use of expired drugs:***

   Conduct physical verification of drug stocks across the country, replace near expiry stocks of Levofloxacin 250 mg with longer expiry stocks and stop using them beyond the expiry date to treat the patients currently on treatment.

   Responsibility: NTP supported by WHO-TL
   Timelines: September 18

K. Recording and reporting, and data management

TL maintains a paper based recording and reporting systems. Paper printouts of forms, registers and quarterly reporting formats for case finding, interim culture conversion and final treatment outcome are sent to the NTP through regional coordinators from the municipalities in aggregate numbers. The NTP also continues to collect and compile the treatment outcomes data from MDR-TB patient cohorts. Although there is QuanTB software available at the central level to facilitate data management for drug logistic, this is only for aggregated data and not a case-based web-based data management system.

Key Observations:

- A paper based TB/DR-TB surveillance system with aggregated reporting is in place except QuanTB for drug logistic management. E/m health solutions not explored in spite of improving penetration of mobile, social media and internet in the country as well as health information systems under development to serve epidemiological intelligence to the programme for policy refinements in future.

Recommendations:

1. ***Digitalize TB for elimination in TL:***

   Harness the penetration of mobile, social media and internet in TL and invest in electronic case based patient tracking and data management system under HMIS to cover e/m health solutions in the whole spectrum of services from health education to test request to results to treatment to adherence monitoring to aDSM to logistic management to e-records and artificial intelligence (AI) for predictive analysis and prompting course correction in the fight to end TB in TL. Complete development and field testing of the electronic real-time case based TB data management and patient tracking system to serve as a robust electronic surveillance system for all forms of TB.

   Invest for nation-wide implementation of this electronic real-time surveillance system for a dynamic epidemiological intelligence system in country to identify hot-spots, cold-spots, track migrants and facilitate rational investments in cost-effective strategies to yield maximum outputs within available resources.

   Responsibility: NTP supported by WHO-TL
   Timelines: September 18

L. Health System, aDSM and TB Preventive Strategies

Key Observations:

- The health system hierarchy from national, regional and municipality level as well as the strengthened primary health care delivery package "Saude na familia" exists as an opportunity for integrating TB care package including the weak aDSM mechanisms and infection control clubbed with community engagement.

- Pre-treatment evaluation and monitoring adverse events in MDR-TB patients particularly with the recommendation of newer anti-TB drugs require further investment in strengthening the laboratories for bio-chemical investigations and specific equipment like ECG, audiometer and ophthalmoscope for ADR monitoring at national, regional and municipality levels.

- Infection control is an integral part of the national TB guidelines. IC interventions for TB are common to and can protect from many airborne infections at various settings. Adequate administrative and personal protective measures observed to be in place at DR-TB center and NTRL visited, however, there remains pertinent challenges to implement infection control posed by need for greater engagement with general health system, the limited access to case finding of infectious pool of patients early from the community and health care facilities described that could be effective tailored to the country specific needs.

- There is a national policy for INH chemoprophylaxis to PLHIV and children < 5 years with limited implementation. There is no clear national policy on detection and management of latent TB infection (LTBI) in the country although this is envisaged in the NSP. Atauro Island off Dili identified as the initial site to be made TB Free, however, no clear strategy available to this effect.

Recommendations:

1. *Design and implement "SnF TB Care Package":*

Develop a comprehensive "SnF TB Care Package" for implementation through Saude na Familia mechanism and engaging the community to cover at least the following activities and services:

i) Mapping vulnerable groups
ii) TB health education including cough etiquette and infection control
iii) Assess Nutritional Status – Height, weight, MAC

iv) Screening (4 symptoms) & referral for LTBI, TB, DR-TB testing
v) Referral for contacts for screening and IGRA
vi) Specimen collection and transport
vii) Arrange & monitor treatment adherence for LTBI, TB, DR-TB, TB-HIV etc.
viii) Adverse event identification and referral to appropriate level
ix) Nutrition and social support
x) Vocational training and employment linkage

Responsibility: NTP supported by WHO-TL
Timelines: December 18

2. Integrate TB Infection Control with active case finding:

Update the infection control guidelines and integrate its implementation through the public health systems with the following specific approaches:

i) Community level – through Saude na familia TB care package
ii) Health facility OPD – cough corner for infection control and case finding
iii) TB IC in wards – ventilation, bed spacing, mask & disinfection spittoon for patient, visitors restricted, N95 mask for staff

Consider training of key architects and engineers involved in the health-care facility designing/renovation to be trained in the international course on building designs and environmental measures for airborne infection control.

Responsibility: NTP supported by WHO-TL
Timelines: December 18

3. Strengthen aDSM system:

Strengthen laboratories at national, regional, municipality and CHC levels to conduct the complete set of investigations required for pre-treatment evaluation and ADR monitoring of TB and DR-TB patients. Equip the DR-TB centers at all levels to monitor ECG, audiometry and ophthalmoscopy for specific ADRs that occur with newer anti-TB drugs. Establish strong referral network with national, regional and municipality level hospitals for specialist consultation, emergency managements and surgical interventions.

Responsibility: NTP, National Hospital supported by WHO-TL
Timelines: December 18

4. *Design and implement "TB Free core package" including LTBI:*

Develop a comprehensive "TB Free core package" to build system capacity for prevention (infection control & LTBI), detection (active case finding for all forms of TB & DR-TB), treatment (appropriate regimen for all forms of TB & DR-TB) and social protection from catastrophic socio-economic effects of TB (addressing needs for nutritional, co-morbidities, migration, travel enablers, insurances etc.) using all available tools for implementation through Saude na Familia mechanism to cover at least Atauro Island off Dili in 2019 and effect learning based scale-up to low burden pockets. The LTBI strategy should be designed in consultation with the national experts to include at least the following:

i) Four symptom (4S) screening, CxR, GeneXpert® among at least contacts of TB patients: children <5 yrs, PLHIV, adults
ii) Identification of LTBI – e.g. IGRA
iii) Treatment of LTBI – e.g. 6HR or 3HP
iv) Adherence monitoring mechanism

Responsibility: NTP, National Hospital supported by WHO-TL
Timelines: December 18

M. Advocacy and community engagement

Advocacy and community engagement is weak in NTP. Though there have been efforts to engage village level leaders, health posts (saude na familia) and religious leaders, but no appreciable outcomes are evident. In fact the case detection rate has fallen by 3% from 57% in 2016 to 54% in 2017. It was learnt from interaction with the programme staff at national, provincial and municipality levels that advocacy and engagement efforts at the community level was undertaken by the health post particularly by 'Saude Na Familia', PSF, SISCa and NGO staff like Klibur Domin, IoM and Caritas while conducting active case finding activities and supervision. This is monitored by the Regional Supervisors as well as the Municipality TB Center (DTC). Specific opportunities and recommendations are covered in the section L above.

N.Supervision and monitoring of the programme

It was informed that the supervision and monitoring functions are undertaken by NTP team, regional coordinators, district TB coordinators and health post staff. Supervisory visits are regularly conducted from each level to the immediate lower level of services by designated supervisory staff. The corresponding laboratory hierarchy from NTRL, to regional, municipality and CHC level microscopy centers for external quality assurance is also functional. At the community level, the SISCa team at health posts

supervise the functions of active case finding and direct observation of treatment at clinic level followed by home visits of patients who do not show up for their daily FDC for first line treatment. It was informed that the annual performance review are also conducted by NTP to review the progress in TB & PMDT services, programme management, case notification and case holding status and administrative issues etc. These processes need to be sustained and strengthened as TL heads towards universal access to quality TB and PMDT services across the country.

O. PMDT plan including funding source (Part of national TB plan or separate)

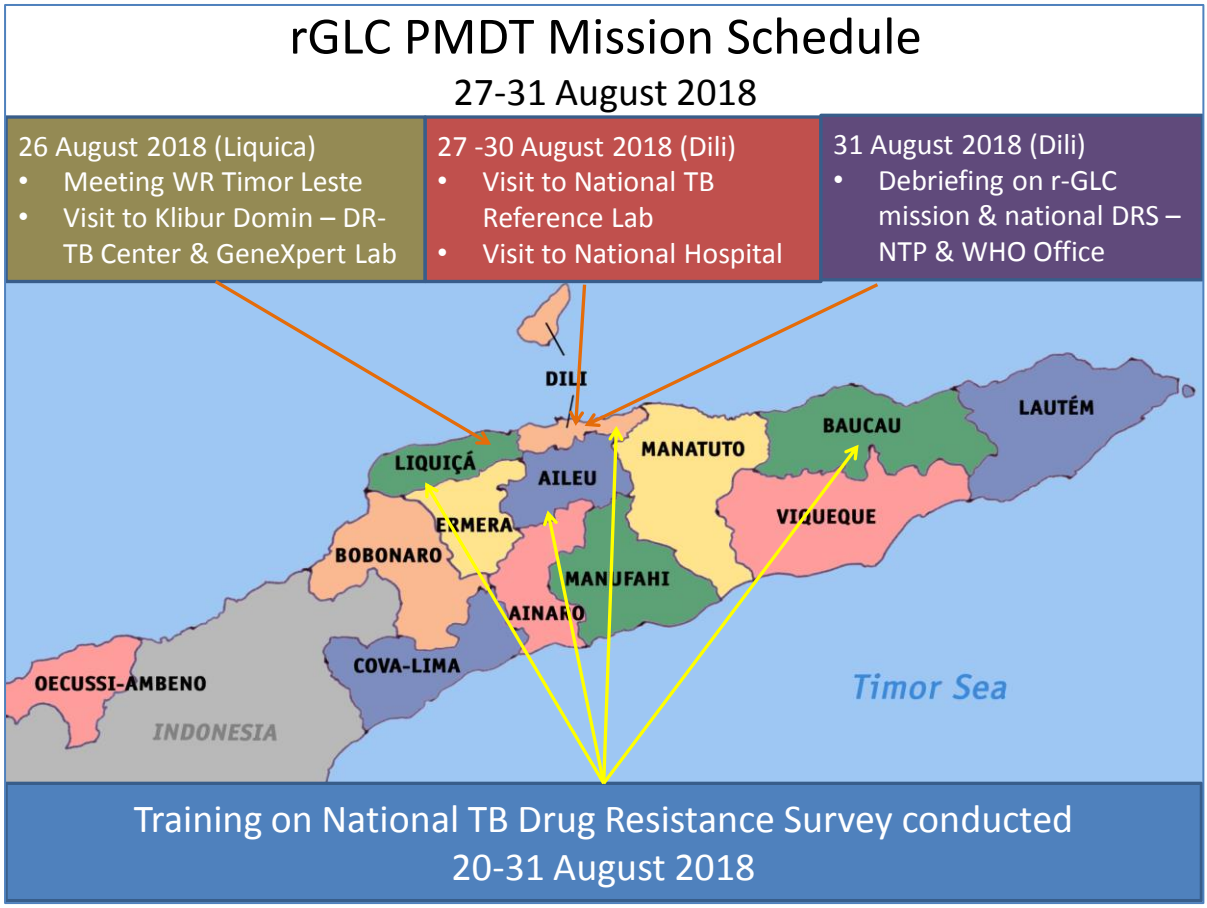
The MoH has developed a PMDT expansion plan within the NSP 2022, however; the national guidelines need to be aligned with the NSP as well as the GF NFM Grant phase II. The NSP needs to be fully funded through sustained international commitment from donors like GF, KOICA, JICA etc. and enhanced domestic contribution as detailed in section C above.

The recommendations were gracefully accepted by the top brass as the author exercised transparency and openness to suggestions from them to enable refinement, improvisation and ownership for enactment.

The NTP and WHO TL also requested the author to continue providing inputs after the mission to finalize the PMDT guidelines including shorter MDR-TB regimen and scale up plans of TL.

Annexure 1 - Summary of activities:

The figure below summarizes the places visited and specific activities undertaken during the mission:



The following stakeholders were met during the mission:

At National TB Programme Office, Dili:

- Sr. Constantino Lopez – NTP Manager
- Sr. Bernardino da Cruz - Regional TB Coordinator
- Sr. Alino Gonzaga - Regional TB Coordinator
- Sr. Oscar Abel da C. Barros Silva - Regional TB Coordinator

At WHO Country Office for TL, Dili:

- Dr Rajesh Pandav – WHO Representative to TL
- Dr Dipanjan Roy – Technical Officer HIV & TB, WHO TL
- Ms Renu Sharma – Administrative Officer
- Ms Da Cruz Vicente, Irene Teresa – Executive Officer
- Dr Yu Dongbao – Medical Officer Epidemiology
- Ms. Imaculada Lobo Belo – Program Associate, Nutrition

At National Hospital, Dili:

- Dr Flavio – Clinical Director
- Dr Sheena, National HIV-AIDS Programme Manager
- Dr Mateus Pinheiro – Specialist Pulmonologist Dr Virna Martins, Senior Pediatrician
- Dr Etelvina de Jesus, Nodal Physician for DR-TB

At National Reference Laboratory, Dili:

- Ms. Joana Dias, Chief, TB Laboratory

At Klibur Domin DR-TB Center & GeneXpert® Lab, Liquica:

- Mr Joaquin Frietas, Director, Klibur Domain
- 4 patients on standard MDR-TB regimen interviewed

At Municipality TB Center, Liquica:

- Mr Fernando da Conceçao, Interim Public Health Director

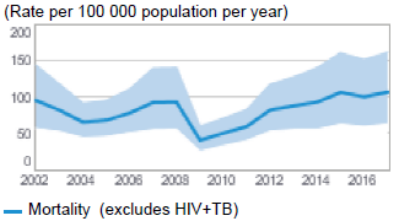
Annexure 2 –Draft TB Profile 2017 – TL:

Timor-Leste

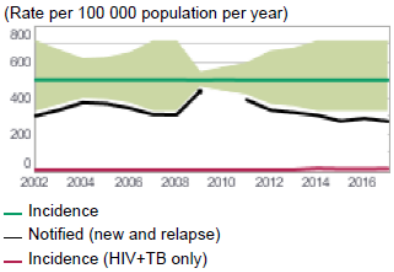
-Draft-Tuberculosis profile

Population 2017 **1.3 million** ***

Estimates of TB burden*, 2017	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	1.4 (0.81–2.1)	106 (63–161)
Mortality (HIV+TB only)	<0.01 (0–0.019)	0.46 (0.03–1.5)
Incidence (includes HIV+TB)	6.5 (4.2–9.2)	498 (322–711)
Incidence (HIV+TB only)	0.059 (0.037–0.085)	4.5 (2.9–6.6)
Incidence (MDR/RR-TB)**	0.26 (0.089–0.52)	20 (6.9–40)



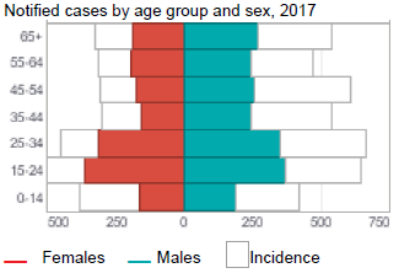
Estimated TB incidence by age and sex (thousands)*, 2017	0-14 years	> 14 years	Total
Females	0.38 (0.34–0.42)	2.2 (1.7–2.7)	2.6 (1.9–3.2)
Males	0.42 (0.38–0.46)	3.5 (2.5–4.5)	3.9 (2.7–5.1)
Total	0.8 (0.69–0.91)	5.7 (3.6–7.7)	6.5 (4.2–9.2)



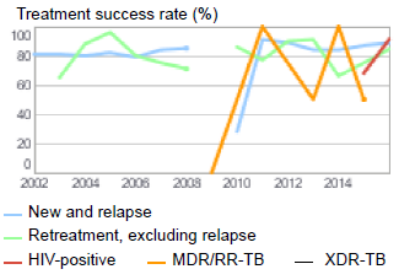
TB case notifications, 2017	
Total cases notified	3 579
Total new and relapse	3 470
- % tested with rapid diagnostics at time of diagnosis	*11%*
- % with known HIV status	*77%*
- % pulmonary	*83%*
- % bacteriologically confirmed among pulmonary	*68%*

Universal health coverage and social protection	
TB treatment coverage (notified/estimated incidence), 2017	54% (38–83)
TB patients facing catastrophic total costs, 2017	83%
TB case fatality ratio (estimated mortality/estimated incidence), 2017	0.22 (0.11–0.36)

TB/HIV care in new and relapse TB patients, 2017	Number	(%)
Patients with known HIV-status who are HIV-positive	25	<1%
- on antiretroviral therapy	*25*	*100%*



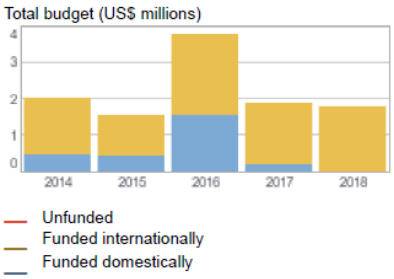
Drug-resistant TB care, 2017	New cases	Previously treated cases	Total number***
Estimated MDR/RR-TB cases among notified pulmonary TB cases			130 (55–200)
Estimated % of TB cases with MDR/RR-TB	3.3% (1.2–6.4)	18% (11–26)	
% notified tested for rifampicin resistance	11%	0%	366
MDR/RR-TB cases tested for resistance to second-line drugs			4
Laboratory-confirmed cases			MDR/RR-TB: 4, XDR-TB: 0
Patients started on treatment ****			MDR/RR-TB: 4, XDR-TB: 0



Treatment success rate and cohort size	Success	Cohort
New and relapse cases registered in 2016	89%	3 718
Previously treated cases, excluding relapse, registered in 2016	85%	13
HIV-positive TB cases registered in 2016	91%	23
MDR/RR-TB cases started on second-line treatment in 2015	50%	4
XDR-TB cases started on second-line treatment in 2015		0

TB preventive treatment, 2017	
% of HIV-positive people (newly enrolled in care) on preventive treatment	
% of children (aged < 5) household contacts of bacteriologically-confirmed TB cases on preventive treatment	96% (88–100)

TB financing, 2018	
National TB budget (US$ millions)	1.8
Funding source: 0% domestic, 100% international, 0% unfunded	



** Ranges represent uncertainty intervals*
*** MDR is TB resistant to rifampicin and isoniazid; RR is TB resistant to rifampicin*
**** Includes cases with unknown previous TB treatment history*
***** Includes patients diagnosed before 2017 and patients who were not laboratory-confirmed*

Data are as reported to WHO. Estimates of TB and MDR-TB burden are produced by WHO in consultation with countries.
Generated: 2018-08-30

Data: www.who.int/tb/data

Annexure 3 – Mapping of updates required in the TB Guidelines (including DR-TB) in TL:

(Integrated Single Guidelines needed)

Illustrative Document, less text heavy needed.

- Training materials may be disintegrated for individual cadres of staff and translated in local language, consider active voice here.
- Detailed National Pediatric TB Guidelines and National EP-TB guidelines recently developed can be aligned with the updated TB guidelines later.

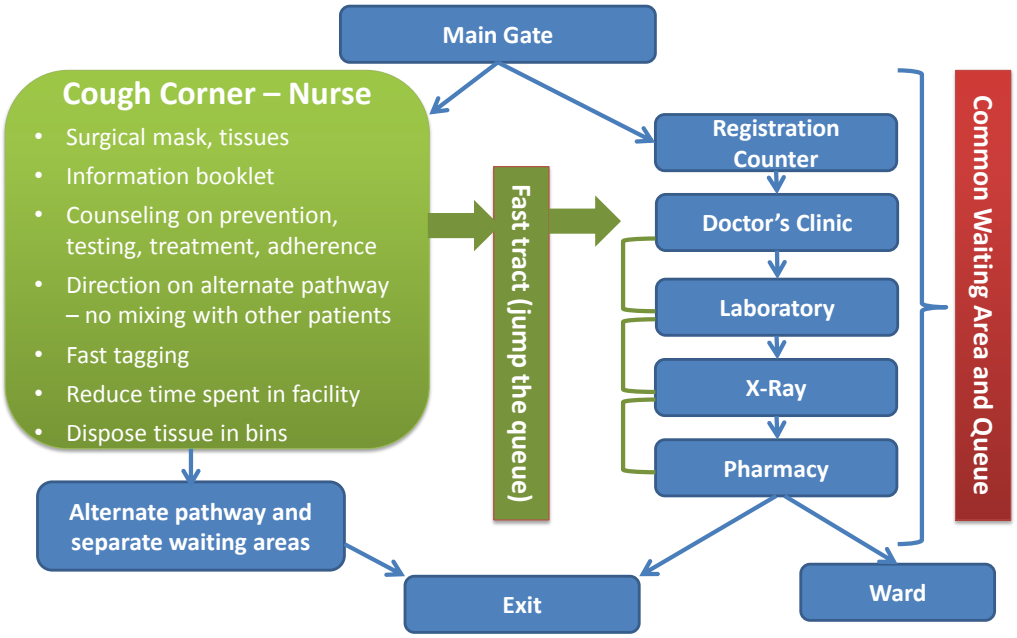
Theme	Reference Documents	Responsible
Foreword	Political statement, major strategic changes, resources, target of end TB	NTP
Introduction (Problem statement and epidemiology - Infection, TB, Co-morbidity & DR-TB cause/response and where we are)	GTB 2018, NSP, Catastrophic survey, KAP survey, co-morbidity (Nutrition, Tobacco, HIV) mention DRS and plans for prevalence survey	NTP & WHO TL
National Strategic Plan (Summarize with result framework and Include Inter-ministerial / multi-sectoral collaboration)	Political statement NSP 2018-22 (including research)	NTP & WHO TL
Structure of the NTP & Partnerships	Existing structure (Public and Private Sector with collaborative mechanism) to be reviewed and ToRs redefined - C-DST Laboratory - Regional Hospital (TOR – Peds, DR-TB, EP-TB, Co-morbidities) - Programme management (NTP, Regional, District, CHC, HP, SAMES etc.) - Saude na Familia (care package for TB & co-morbidities) - Staffing and Training Mandates for TB notification by private sector and public health action End with collaborative and synergistic mechanisms	NTP & WHO TL

Prevention of TB (TB Infection Control, LTBI, Prophylaxis, BCG Vaccination, Bio-medical waste management)	Current Global & National BMW Guidelines	WHO TL, NTP, rGLC team
Case Finding and Diagnostic services (Active Case Finding in prioritized clinically, socially, geographical vulnerable group – at community [saude na familia] as well as health care facilities [cough corners – IC & CF], UDST & Presumptive DR-TB testing with FL & SL-DST, Diagnostics network and technologies, specimen collection packaging transport disposal, EQA brief, Case Definitions, Diagnostic Algorithms for TB, DR-TB)	Current Global Guidelines Screening tools (4 symptom screening, Digital CXR) Latest Guidelines on available technologies (Microscopy, GeneXpert®, Solid Culture) and future lab expansion plan (MGIT, LPA, TB LAMP)	WHO TL, NTP, NRL, rGLC team
Case Management – TB, DR-TB (goals, classification of patients, classification of drugs, pretreatment evaluation, regimens – DS, H mono/poly, RR-TB, Pre-XDR, XDR), dosages by weight bands, counseling patients and family, patient flow for treatment, criteria for hospitalization, nutrition, quit tobacco advise, social-economic support, support adherence monitoring, enablers, follow up schedules, monitoring progress on treatment, retrieval of treatment interrupters, treatment outcome definitions	Current Global Guidelines Regimens, dosages, weight bands for DS-TB, H mono/poly, MDR/RR-TB, MDR/RR-TB (FQ/XDR) in line with 2018 WHO guidelines. 99DOTS, Pill box (China) etc. to be considered to substantiate adherence monitoring and retrieval (family member, community, health provider) – accessible and accountable to the system	WHO TL, NTP, NH, rGLC team
TB Co-morbidities & Special Situations (Collaborative mechanisms, Diagnosis, treatment, prevention and support to be covered for TB-Malnutrition, TB-Tobacco, TB-HIV, TB-DM, TB-Hepatitis, other systemic diseases etc. Brief sections on Pediatric TB, Pregnancy, EP-TB. MDR-TB in special situations)	Current Global Guidelines Current National strategies for co-morbid conditions, provisions and services for each of the conditions and integration opportunities	WHO TL, Specialists from National Hospital, National programs (TB, HIV, Nutrition, NCD), rGLC team

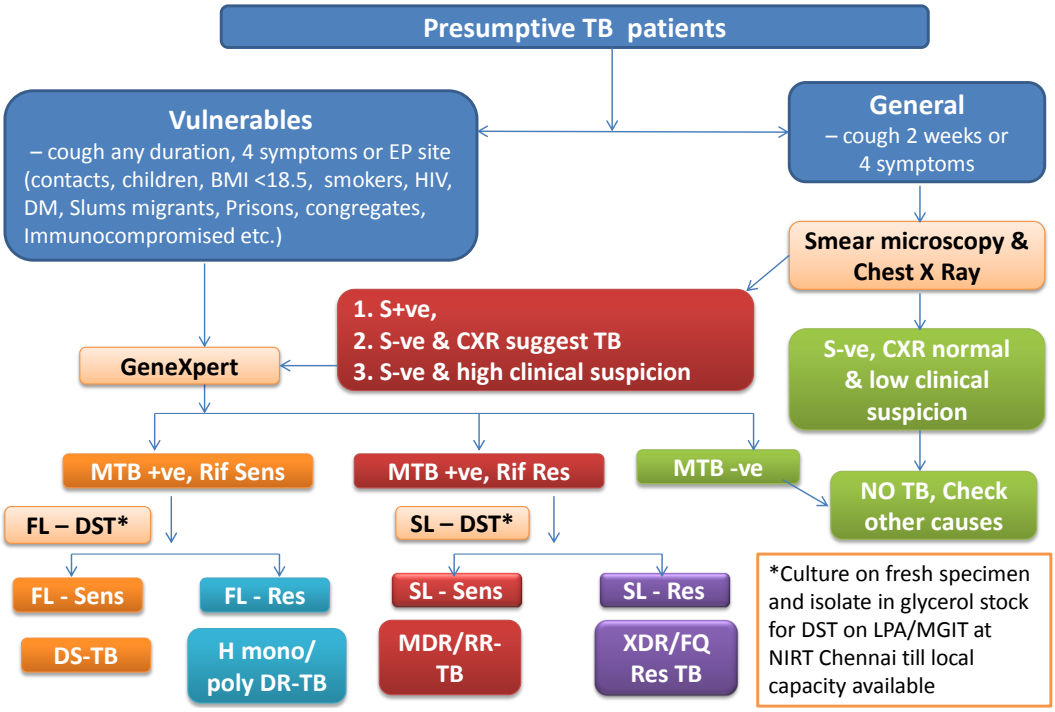
Active Drug Safety Management and Monitoring (First & Second Line Drugs – common adverse events and serious adverse events with offending agents known, early identification, referral and management strategies for each type of adverse event, reintroduction of drugs after adverse event or hypersensitivity reaction, recording and reporting systems for adverse events)	Current Global Guidelines for Treatment of TB, DR-TB and aDSM	WHO TL, NTP, NH, rGLC team
Procurement supply chain management for TB diagnostics and drugs (Flow of diagnostics and Drugs from SAMES to Labs and treatment centers and monitoring)	SAMES background, functions and services Product list, quality assurance, formulations from GDF website Gx Alert for monitoring Gx tests, maintenance and consumables QuanTB for supply chain management monitoring	WHO TL, NTP, SAMES, rGLC team
Recording and Reporting (Paper based formats, flow of information, process of data management)	Current Global Guidelines for R&R Opportunities for online case based patient tracking system in future	WHO TL, NTP, rGLC team
Supervision, Monitoring, Evaluation (including indicators)	Current Global Guidelines, End TB Strategy National Strategic Plan	WHO TL, NTP, rGLC team
Health Education, Advocacy, Communication, Social Mobilization (Develop pictorial/simple materials for health education communication and social media. Define a clear communication strategy for advocacy with higher officials & donors, with health care providers, patients and communities aligned to the new guidelines)		WHO TL & NTP.
Operational Research (mechanism, research priorities, provisions from programme)		WHO TL & NTP
Annexures, Tables, Figures to be updated		WHO TL & NTP

Annexure 4 - Proposed Active Case Finding with Infection Control in Health Care Facilities; Diagnostic Strategy and Algorithm for TL:

Cough Corner at Health Facility OPD
– For Infection Control and Active Case Finding



Diagnostic Strategy & Algorithm



Annexure 5: Detailed report on Lab assessment and National DRS trainings:

Two weeks' visit was undertaken to Timor-Leste for training and preparations for TB DRS from 19th August 2018 to 31st August 2018. Three training programmes were conducted at District levels as per the following schedule:

Sl.No	Dates of Training	District
1	20th -21st August 2018	Baucau
2	23rd -24th August 2018	Alieu
3	27th -28th August 2018	Liquica

Training material developed by the NTP was used for all the schedules. During the training, the participants were sensitized on the DRS, its purpose, methodology and operating procedures and quality assurance protocols. Demonstration of Specimen collection, packaging and transport was carried out at each training venue, followed by Hands on practice by the participants. Role plays were also carried out for patient interviews, during the training. It was observed that a few modifications were required in the procedures laid down for the DRS. The details of which along with the recommendations are given under a separate heading in the later part of this report.

The National Laboratory was visited from 29th August to 31st August 2018. The laboratory procedures, infrastructure and consumables available were observed and verified. Laboratory procedures for the DRS were discussed in detail. Preparation of Glycerol Stock suspensions was explained and the procedure annexed (**Appendix I**). The correct method to perform GeneXpert® test was demonstrated to the technicians. Preparation of 5% phenol disinfectant solution was also demonstrated. The key observations at the National laboratory and recommendations thereof are as below:

Observation	**Recommendation**
Falcon Tubes were in short supply	To procure Falcon tubes and use for sputum collection and transport as well as for performing GeneXpert® test.
Inspissators were placed in level II area and not made functional.	Inspissators may be shifted to the media room. One of the Inspissators was set up during the visit and the procedure demonstrated.
Halogen Lamp was not available for Culture reading	A table lamp with 100W halogen bulb may be provided for Culture reading.
Washing area is currently co-located in the Media preparation room. No separate area is available for sterilization.	A separate area may be identified for washing and sterilization, in the ground floor of the laboratory. This room is to be equipped with Washing sinks, exhaust fans, Autoclave, Hot air oven and a Geyser.
ICT kits not available	Since the laboratory does not perform biochemical tests for species identification, ICT Kits are essential for *M.tb*

	identification.
Middlebrooks 7H9 broth and supplement are not available	To procure Middlebrooks 7H9 broth and supplement for making Glycerol stocks and onward transport to the SNRL.
Bio Bottles for specimen transport is in short supply	To reconcile existing stocks and indent the required quantities. Approximately 20 strains are ideal to be prepared and sent in a single consignment.
GeneXpert® tests were not being performed as per procedure. Buffer was being added to sputum containers using pasture pipette, no shaking or vortexing was done.	Correct method of testing was demonstrated using Falcon tubes, shaking for twenty times *etc.,* training Videos were also provided.
Disinfectants are not being prepared and distributed.	Preparation of 5% disinfectant using crystalline phenol was demonstrated.
Bio Medical Waste Management not being practiced. Disinfected and autoclaved wastes are thrown out in the open.	It is essential to have a robust BMW system in place. Sputum cups are not to be burned. The disinfected wastes are not to be thrown in the open. Options of centralized collection and disposal; constructing deep burial pits *etc.,* may be explored.
There are no Stock registers and no inventory management for the laboratory supplies and equipment.	It is very important to have an inventory of supplies to the laboratory. Estimations of material needed and reconciliation of the existing stock would otherwise become a practical impossibility.
Glassware and regular use lab consumables are either not available or in short supply.	Basic essential Glass wares are to be made available at the National laboratory. *A strong leadership is required at the National laboratory to forecast the requirements, oversee correctness of procedures and guide the technicians.*

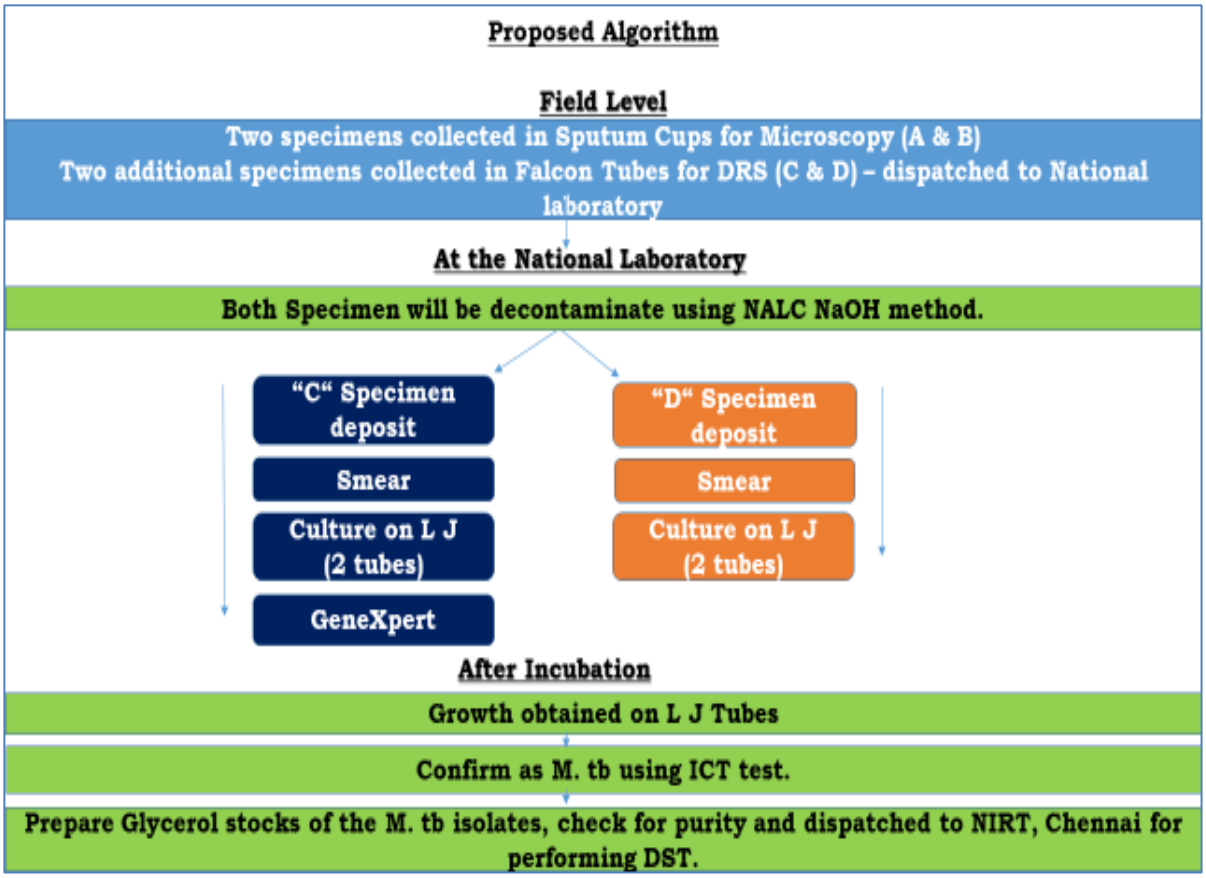
Observations and recommendations (including minor revisions) for DRS.

Observation	Recommendations
The current protocol indicates that the remnant portion of specimen collected for Microscopy be stored in the refrigerator, transported to the district where they are packaged and stored for dispatch on scheduled days a week to the National Laboratory.	It is not a good laboratory practice to send the remnant portion of specimen collected for Microscopy to the National Laboratory. The specimen container has already been opened and thus potential contamination can occur, more so since it will be stored for days together before dispatch. It is therefore suggested that two additional specimens be collected for the DRS from the smear positive patients and dispatched soon after collection directly to the National laboratory.
As per the current protocol Specimen are to be	It is preferable to use 50ml polypropylene centrifuge tubes (*e.g.,* Falcon tubes) for collection, packaging and

collected in sputum cups , packaged and transported.	transport of sputum specimen. The advantages that are offered include that the shape and size of the Falcon tubes make the packaging more convenient, if the caps are secured tightly, Falcon tubes are leak proof, the tubes can be readily centrifuged (for digestion & decontamination), and the graduations allow addition of correct quantities of reagents.
The secondary container in the triple layer packaging does not indicate absorbent material.	A layer of absorbent cotton is to be placed around the tubes as per the guidelines for specimen transport. The procedure has been demonstrated during the trainings. A copy of the WHO Guidelines for Transport of biological specimen, is attached with this report for reference.
The protocol indicates that GeneXpert® will be performed on one of the specimen. The other specimen will be aliquoted and one aliquot processed for culture and the other sent to SNRL – NIRT, Chennai, India for Culture and DST. Sputum specimens have been sent earlier to NIRT Chennai. Records were not available for the details of the same, delay in transit and recovery rates were also not recorded at the National laboratory. Upon telephonic discussions with the Microbiologist at NIRT, it was learnt that the transit time was 27- 30 days. The culture recover rate was only 29%.	It is proposed that the National laboratory will decontaminate the both the specimens (NALC NaoH). (procedure annexed - **Appendix II**). The decontaminated sediments will be used for preparing smear and for inoculating Culture tubes. Readymade L J tubes (Difco) may be procured and used. This will obviate the need to manufacture media in the laboratory. 0.5 ml of one of the sediments will be used for performing GeneXpert® test. (procedure annexed - **Appendix III**). The growth obtained on Culture will be confirmed as *M. tb* using ICT test. Glycerol stocks will be prepared of the *M. tb* isolates, checked for purity (Nutrient Agar plates to be borrowed from Microbiology department in the same premise) and dispatched to NIRT, Chennai for performing DST. ***Detailed Algorithm is provided below the table***. The proposed revision has been discussed telephonically with Dr. Radha Krishnan, Dr. Gomathi and Dr. Siva Kumar from NIRT and agreed upon. At NIRT, Chennai Liquid Culture and DST will be performed for - Streptomycin, Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Ofloxacin, Levofloxacin, Moxifloxacin, Kanamycin, Amikacin, Capreomycin, Ethionamide, PAS, Linezolid and Clofazimine
Certain consumables and accessory laboratory items are not available for the laboratory procedures.	The list of requirements is given below separately.

Other recommendations:

- Appointment of Consultants for Microbiology and Data Management needs to be done at the earliest.
- The laboratory technicians at the National Laboratory require to undergo a refresher training focusing on in LJ preparation, inoculation, culture reading, ICT testing and Glycerol stock preparation, before the commencement of the DRS.
- Periodic visit by external TA for support and guidance.



Additional Requirements for the DRS:

SN	Item	Quantity required
1	50 ml Polypropylene screw capped conical tubes (Falcon Tubes)	3000 Nos.
2	ICT Kits	2000 Nos.
3	Middlebrooks 7H9 Broth base (Himedia)	500 Gms.
4	ADC Supplement (Himedia)	20 Vials
5	Readymade LJ Tubes (Difco); this is Optional- subject to availability of funds (if used will significantly reduce laboratory time and effort)	4000 tubes
6	Bio Bottles for transport – Requirement 50 bottles	To be reconciled with existing stock
7	Sodium Citrate	500 Gms.
8	Other laboratory consumables and glassware	To be reconciled with existing stock

<u>Appendix I</u> - Preparation of bacterial suspension for transportation:

Using a wire loop (SWG24, 3mm internal diameter), take a representative sample of approximately 2/3rd loopful (4-5 mg) from the primary culture and place in a Bijou bottle containing 1 ml sterile distilled water (SDW) & 3-4 glass beads of 3 mm diameter.

↓

Vortex the bottle for 20–30 seconds; slowly add 4-5 ml of distilled water with continuous shaking.

↓

Leave the suspension on the bench for 15- 20 minutes to allow the coarse particles to settle down.

↓

Decant the supernatant carefully into another clear, sterile Bijou bottle.

↓

Adjust the opacity of the bacterial suspension by the addition of distilled water to obtain a concentration of 1 mg/ml of tubercle bacilli (by matching with McFarland standard No.1)

↓

Prepare 7H9 broth as per the manufactures instruction and autoclave it. After it has been autoclaved, let it cool down. Add the required amount of ADC to the broth as per the manufactures instructions.

↓

Incubate the entire flask at 37deg C for 48hrs and observe for turbidity. Use it only if the solution appears clear.

↓

Take 500 µL of the 7H9 broth in a sterile 2ml screw cryovial. Label the cryovials with appropriate culture isolate number

↓

To this add 500 µL of the bacterial suspension. Close the vials tightly and incubate at 37degC for 3 days.

↓

After 3 days do a sterility check by inoculating on nutrient agar. (1 loopful of the growth from the cryovial onto the nutrient agar slopes) and incubated at 37deg C for 48 hrs.

↓

If there is no growth, it indicates that the cultures in the vials are pure and free from any bacterial contamination.

↓

Add one drop of 50% Glycerol (*see procedure for preparation given below*) to the cryovials using a sterile single use graduated pasture pipette. The cryovials are now ready to be packaged for transportation. (*see procedure for packaging and Transport given below)*

Preparation of 50% glycerol:

- *Prepare 50% glycerol solution by diluting Glycerol in distilled water.*
- *For preparing 50 ml (of 50% Glycerol), take 25ml of distilled water in a sterile 100ml conical flask.*
- *To this add 25ml of Absolute Glycerol by using a sterile 50ml measuring cylinder. Glycerol is highly viscous and hence measure and pour carefully.*
- *Stir the water and Glycerol mixture using a glass rod and ensure that the solution is uniform.*
- *Label the conical flask as 50% Glycerol. Plug the conical flask using cotton buns and autoclave.*
- *50% Glycerol should be autoclaved at 121°C, 15 lbs with a holding time of 20mins.*
- *The solution can be aliquoted as 10ml or 5ml tubes and stored for up to 6 months at 4°C.*

Packaging for transportation:

- Cut a small piece of Para film to seal the cap - neck interface of the cryovial.
- Apply the Para film by stretching it and carefully wrapping it around the cryovial. Ensure that the Para film is applied in the same direction as the cryovial cap is tightened. (*If it is done in the opposite direction, the cap will get loosened and lead to leakage of sample*).
- Wrap the cryovials with a thin layer of absorbent cotton and place them in a zip lock cover. Remove the air in the cover and apply the zip lock. Wrap the cover around the cryovials and secure using rubber bands.
- Multiple such packets could be placed in another zip lock cover and sealed.
- Place the cover containing the cryovials in a sturdy container with frozen gel packs for shipment.
- The package which is to be shipped should contain the name and address of the receiving and dispatching laboratory along with the "**Biohazard**" sticker.
- Ensure that the document for transporting infectious material is filled as per your Government regulations.

Appendix II - Reagents required for Sputum specimen processing:

Reagent A: 4% NaOH:
Dissolve 4g of NaOH pellets into 100ml of distilled water, distribute 50 ml each in two flasks and autoclave.

Reagent B: 2.9% Sodium citrate Solution:
Dissolve 2.9g sodium citrate into 100ml of distilled water, distribute 50 ml each in two flasks and autoclave.

Procedure:
Mix equal quantities of the **Reagent A and Reagent B** just before to use. Prepare in small volumes (only as much volume as can be used in a day). Add NALC powder to achieve a final concentration of 0.5% (*i.e.,* 100ml of NaOH-Sodium citrate solution + 0.5g NALC powder), and mixed well. NALC activity is lost after 24 hours of preparation. The solution cannot be stored and is to be prepared fresh on the day of use.

Phosphate buffer (pH 6.8, 0.067M):

- **Solution A:**
  Dissolve 9.47g of anhydrous disodium phosphate (Na_2HPO_4) in 1000 ml distilled water, using a volumetric flask.

- **Solution B:**
  Dissolve 9.07g of mono potassium phosphate (KH_2PO_4) in 1000 ml distilled water, using a volumetric flask.

Procedure:
Mix equal quantities of the two solutions (A & B). Check pH and balance by using Solution A to raise and Solution B to lower it. The final pH should be 6.8. Sterilize the solution by autoclaving.

Procedure for Sputum Specimen processing using the NALC NaOH method:

Add NaOH-NALC-Sodium Citrate solution in equal volume to that of the specimen and tighten the cap of the Falcon tube

↓

Vortex for 15-30 seconds. Invert the tube gently so that the whole content of the tube is exposed to the NaOH-NALC-Sodium Citrate solution

↓

Wait for 15-20 minutes after adding the NaOH-NALC-Sodium Citrate solution

↓

Vortex lightly every 5-10 minutes. Check for complete liquefaction of the specimen.

↓

If still mucoid, add a small quantity of NALC powder (30-35 mg) directly to the specimen tube and mix well

↓

After 15-20 minutes, add phosphate buffer (pH 6.8) up to the top ring on the centrifuge tube. (**Sterile distilled water should not be used as an alternate for the buffer)*

↓

Mix well by vortexing, Centrifuge at 3000g for 15 to 20 minutes

↓

Allow tubes to stand for 5 minutes after centrifugation, for aerosols to settle down

↓

Without disturbing the sediment, carefully decant the supernatant into a discard jar containing 5% phenol

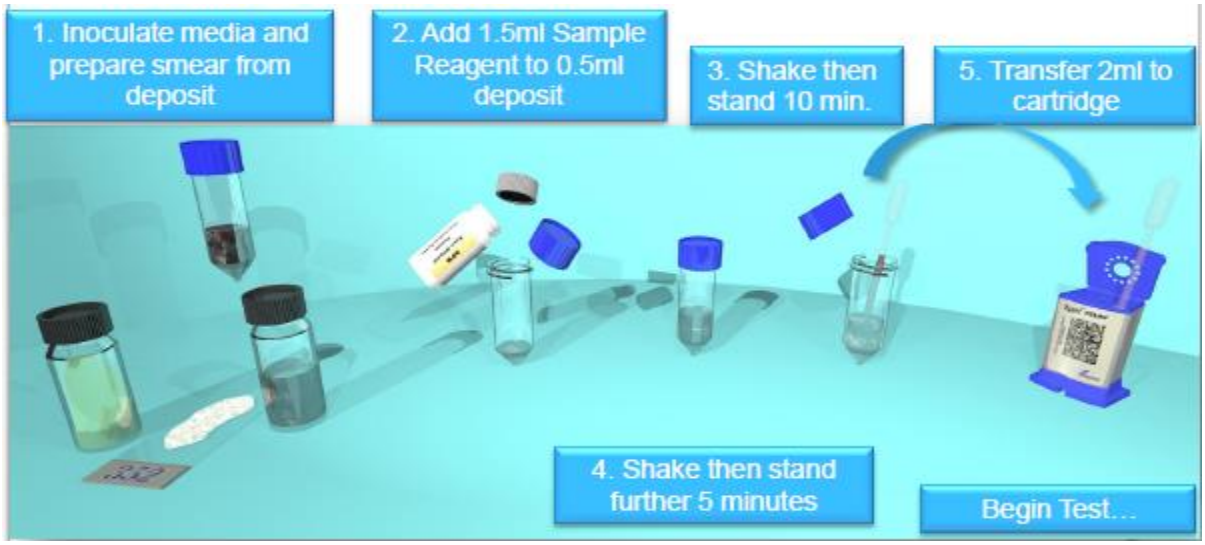
↓

Add 1-2ml of phosphate buffer (pH 6.8) to re-suspend the sediment and vortex

↓

The re-suspended pellet is used to make smears, inoculate culture media and for GeneXpert® testing.

<u>Appendix III</u> - Sample preparation: processed sputum sediment



Annexure 6 – Proposed treatment regimen alignment with latest WHO recommendations and decentralized model of care:

Drug susceptibility	Proposed Regimen
Drug Sensitive TB	2 HREZ / 4 HRE No CAT II regimen
H mono/poly DR-TB	6 REZLfx
MDR/RR-TB	6 Bdq, 6-8 Lfx Lzd Cfz Cs E / 12 Lfx Cfz Cs E
XDR / $MDR_{FQ/SLI}$	6 Bdq, 6-8 Mfx^{h} Lzd Cfz Cs E /12 Mfx^{h} Cfz Cs E OR Individualized

- Pre-treatment investigation, follow up schedule to be considered during guidelines update
- Extension of intensive phase to be based on follow up culture results
- $MDR_{FQ/SLI}$: MDR/RR-TB with additional resistance to FQ or SLI class of drugs