

rGLC COUNTRY SUPPORT MISSION REPORT

Country: Democratic Peoples' Republic of Korea

Inclusive dates of mission: 23-30 October 2018

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The programme has agreed with open sharing of this report



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Abbreviations and acronyms

ADR	Adverse drug reaction
aDSM	active drug safety monitoring and management
AFB	acid-fast bacilli
CFK	Christian Friends of Korea
CPT	Co-trimoxazole preventive therapy
sTPI	county TB preventive institute
CTPI	City TB preventive Institute
DGHS	Director General of Health Services
DOTS	Directly observed therapy – short course
DRS	Drug resistance survey/surveillance
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
EBF	Eugene Bell Foundation
EQA	External quality assurance
FDC	fixed-dose combination
FLD	First-line (anti-TB) drugs
GDF	Global (TB) Drug Facility
GF	Global Fund (Global Fund to Fight AIDS, Tuberculosis and Malaria)
HRD	Human resource development
IC	Infection control
IPT	Isoniazid preventive therapy
IC	Infection control
MDR-TB	Multidrug-resistant tuberculosis
M&E	Monitoring and evaluation
NRL	national TB reference laboratory
PMDT	programmatic management of drug-resistant tuberculosis
PTPI	Provincial TB preventive Institute
RR	Rifampicin-resistant (tuberculosis)
RTRL	Regional TB reference laboratory
SEAR	South-East Asia Region (of WHO)
SLD	Second-line anti-TB drugs
SOPs	Standard operating procedures
TA	Technical assistance
TB	Tuberculosis
WHO	World Health Organization
XDR-RB	Extensively drug-resistant TB

Executive summary

i. TORs of the mission

- To review progress made in scaling-up of PMDT activities and specifically implementation status of recommendations from last rGLC mission, and to provide recommendations for expansion providing different scenarios with and without availability of international funding
- To discuss procurement of lab supplies specifically current needs and estimated requirement in future, and how an uninterrupted supply may be ensured
- Review DR-TB expansion plan, funding needs and anticipated gaps. Make recommendations on possible scenarios for future need
- Hold a consultative meeting on the latest update to WHO DR-TB guidelines/ recommendations
- Assess capacity building/ training needs and TA support needs in future
- Hold a consultative meeting with EBF/CFK/SNRLs (and any other agency considered important) on possible support available, subject to their presence in the country.

ii. Overall implementation status of PMDT

The trend so far has been an overall increase in number of TB and MDR-TB cases being diagnosed and put on treatment. For DS TB, there has been a decline in number of cases notified between 2016 and 2017. This has been attributed to extreme winter in the year.

Table 1: Notification and TB and RR/MDR-TB cases since 2012

	2012	2013	2014	2015	2016	2017
Notified TB cases	99,399	104,912	110,290	120,722	120,323	107,103
% new TB cases tested for RR		0	0	0	0	-
% previously treated TB cases tested for RR	0	1	2	2	8	14
Notified MDR/RR-TB cases	25	244	197	209	935	1515
Patients started on MDR-TB treatment	50	170	212	125	814	1,732
MDR/RR-TB cases in t/t outcome cohort	50	170	212	325		
Estimated MDR/RR-TB among notified pulmonary TB cases						4100

iii. Significant achievements since last visit

- 11/12 provinces covered with PMDT services (increasing from 9 last year). 12th province expected to be covered next year
- Notified previously treated cases tested for rifampicin resistance increase from 8% to 14%.

- Laboratory confirmed cases increased from 935 to 1515
- Patients started on treatment increased from 814 to 1732
- Local data being generated for adverse events among RR/MDR-TB patients
- Ongoing OR on all-oral shorter regimen in collaboration with international agencies

iv. Key challenges identified in this mission in relation to the ToRs

- Uncertain future of funding from donors is adversely impacting the services for TB and MDR-TB. there is uncertainty of securing treatment for already diagnosed both drug sensitive TB and MDR patients and further diagnosis of new patients
- There is an estimated gap annual gap of more than USD 40 million as per the country National Strategic Plan
- In addition to funding issues, country faces challenges with import of consumable and drugs due to sanctions. Several items have faced delays at ports in neighboring countries
- Inability to ensure continuity of treatment for DR-TB patients or improper treatment due to inability to diagnose baseline resistance may lead to amplification of resistance.

v. Priority recommendations of the mission:

Recommendation	Responsible persons/agency	Timeline	Support required to fulfil the recommendation
Adoption of priority approach for GeneXpert cartridge use (explained in narrative below) and simultaneous process of license renewal for full need	NTP/MOPH	Ongoing	WHO, UNICEF and partners to support license renewal
Upgrade the capacity of RRL laboratory at Hamhung to perform DST along with culture in solid media and LPA.	MOPH	Not assigned because of funding situation	Support in mobilisation of resources
Phase out the use of Cat II regimen	MOPH and partners	Immediate	
Adopt all-oral regimen for RR/ MDR-TB patients	MOPH and partners	By end Q 1 2019	Transition planning
Attempt to access free bedaquiline through GDF	MOPH, GDF, WHO and UNICEF	Immediate	EBF has an established channel that could be tapped
Monitoring and management of adverse events as per aDSM guidelines <ul style="list-style-type: none"> • Forms for monitoring and reporting • Systematic data collection • Capacity building 	NTP/MOPH	Q 1 2019	Capacity building workshop
Streamlining procurement and import of essential diagnostics and drugs	Partners – UN bodies, EBF, CFK	Q 1 2019	

Increased domestic resource allocation for TB control	MOPH	Q 1 2019	
Explore additional international funding sources	International agencies	Ongoing	Continuous needs assessment and advocacy
Capacity building needs <ul style="list-style-type: none"> Laboratory C&DST at NTRL and RRL Clinical training aDSM training 	NTP/MOPH	Q1 and Q2 2019	Support from WHO and partners

vi. Status of priority recommendations of previous mission:

Recommendations	Status
Pursue highest level advocacy to resolve procurement bottlenecks to resume PMDT services in DPRK	<ul style="list-style-type: none"> The nature of problem with procurements has changed now
Expedite activities or urgently re-programme to utilize the provisional savings in the current TGF grants	Not relevant
Know your DR-TB epidemiology to prompt local epidemiology guided cost-effective strategies	<ul style="list-style-type: none"> Planned, once the funding situation improves
Complete the draft of PMDT guidelines for DPRK within next 30 days and share with WHO SEARO and the author for inputs and finalization within 2017 after incorporating the decision taken in the workshop	<ul style="list-style-type: none"> The PMDT guidelines need further update with recent WHO recommendations
Refine the NSP and GF proposal to address the inputs provided during the mission	Not relevant
Expand PMDT services in stages to achieve universal DST in DPRK by 2021	Significant progress in last year. However, future of expansion is uncertain
Complete preparation to introduce shorter MDR-TB regimen and newer drugs	<ul style="list-style-type: none"> Preparation underway. Future course depends on adoption of new guidelines and funding available
Build capacity of Laboratory Network in DPRK	<ul style="list-style-type: none"> Ongoing. Challenged by lack of laboratory consumables for C&DST and molecular tests

Achieved	
Some progress/ ongoing	
No change	

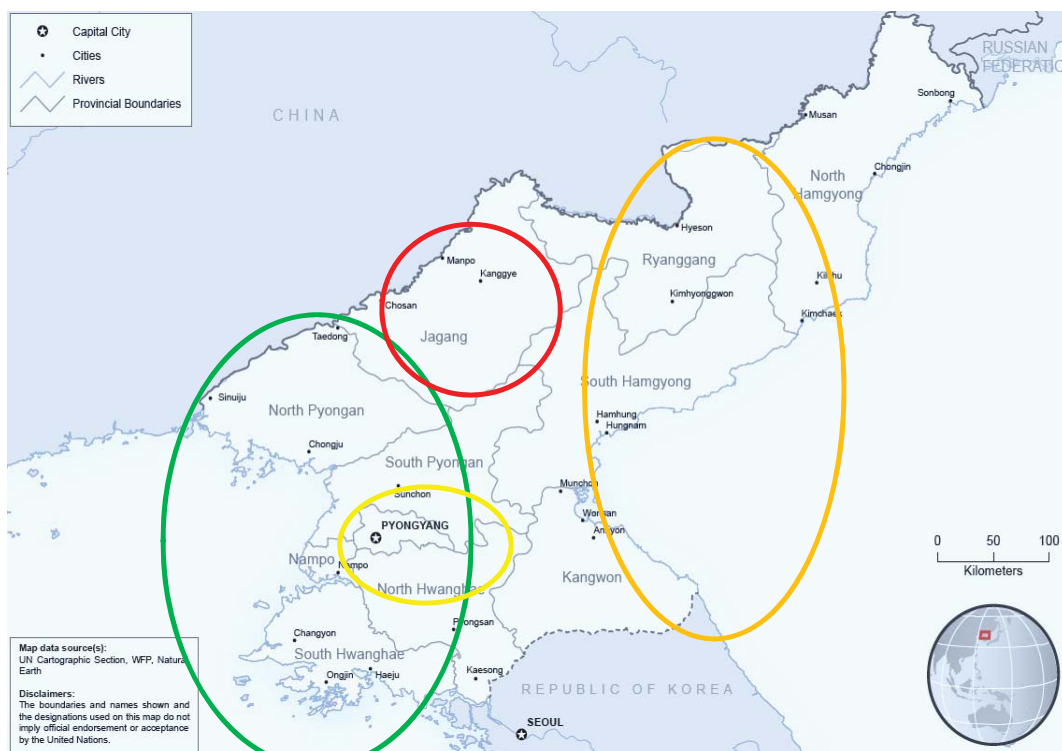
Detailed report

A. Introduction/Background

In DPR Korea, there are 9 provinces and 3 municipalities. The provinces are subdivided into 209 counties/cities/districts. As per Census 2013, the country population is 24,624,639.

MOPH has covered 11 of 12 provinces under MDR-TB services with support from the Global Fund (GF) and Eugene Bell Foundation (EBF). The map below attempts to give a visual impression of the coverage areas within the country

Figure 1: Map of DPR Korea with indicative support from various agencies for MDR-TB services

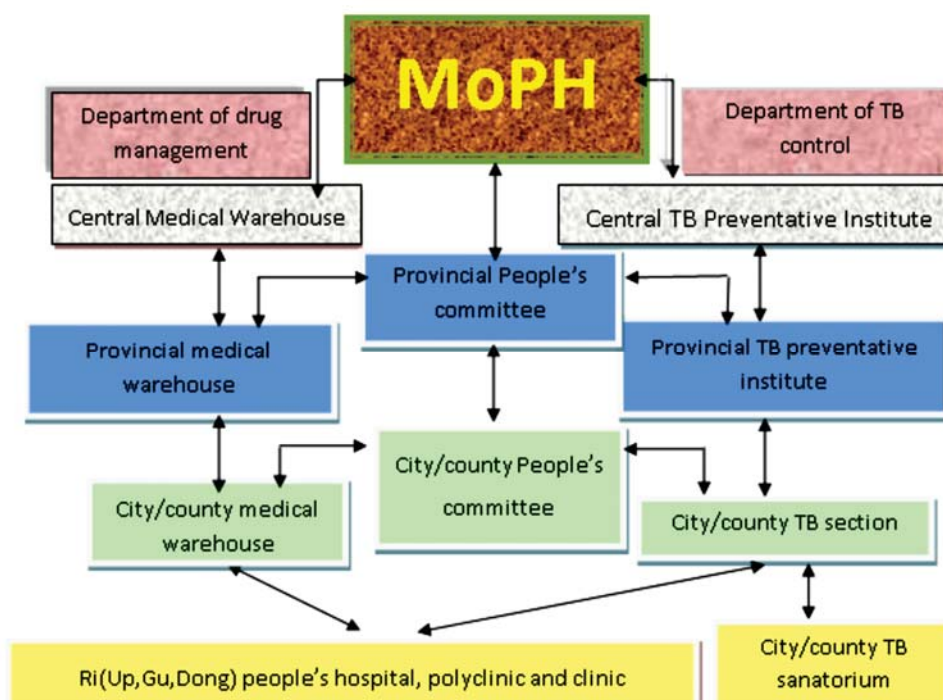


Green: Eugene Bell Foundation, Orange: Global Fund, Yellow: Both GF and EBF, Red; Not covered

Table 2: Coverage of provinces and cities with MDR-TB services and corresponding support

	Name of Province	Population	West coast/East coast /In land area	Coverage support
1	Pyongyang city	3194814	In land	MoPH/ both EBF and GF
2	South Pyongan Province	3164686	West coast	MoPH/EBF
3	North Pyongan Province	2839589	West coast	MoPH/EBF
4	Jagang Province	1358116	In land	not covered
5	South Hwanghae Province	2432669	West coast	MoPH/EBF
6	North Hwanghae Province	2436552	In land	MoPH/EBF
7	Kwangwon Province	1546124	East coast	MoPH/GF
8	South Hamgyong Province	3155798	East coast	MoPH/GF
9	North Hamgyong Province	2217524	East coast	MoPH/GF
10	Ryangang Province	749664	In land	MoPH/GF
11	Nampho city	1024565	West coast	MoPH/EBF
12	Rason City	207597	East coast	MoPH/GF
		24,327,698		

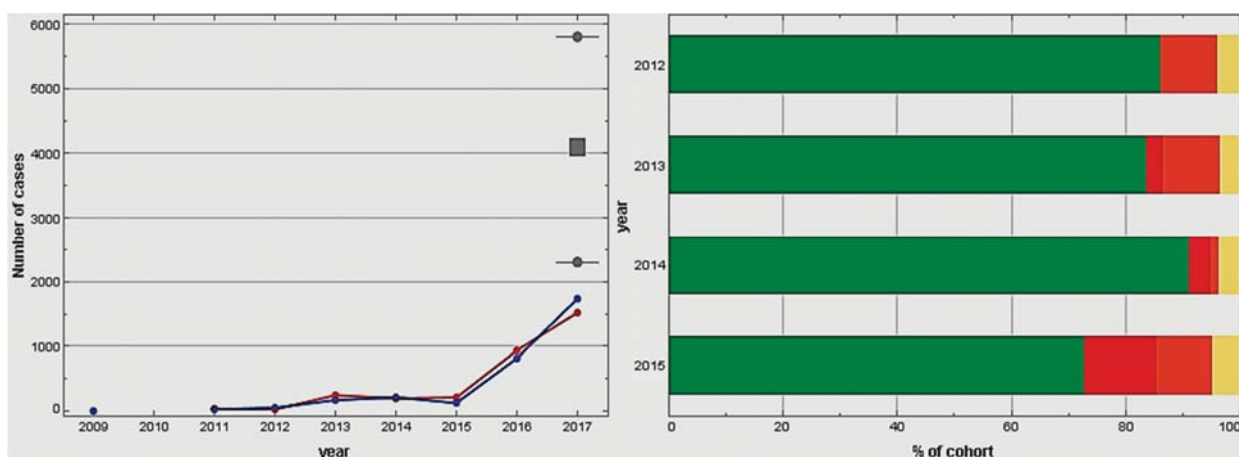
Figure 2: Structure of the TB programme in DPR Korea



B. Overall DR-TB programme performance

There has been a steady increase in detection and enrolment of cases specifically from 2015 onwards reaching 1732 cases in 2016, although it is still less than the target of 4100 estimated RR/MDR-TB cases among the notified pulmonary TB cases. Treatment success rate was steady at more than 80% till 2016 (2014 cohort). However, the treatment success rate has declined to about 72% for the 2015 cohort. This may also be seen because there is a mismatch between the number of cases originally reported to WHO (125) as being put on treatment and those for whom the treatment outcome is reported (325)

Figure 3: Notification and treatment outcome trends



It is also observed that proportion of notified previously treated cases tested for rifampicin resistance has increased from 8% to 14% over past year, laboratory confirmed cases increased from 935 to 1515 during the same period and patients started on treatment increased from 814 to 1732. The reasons for number of patients started on MDR-TB treatment being more than those reported as diagnosed could be due to – some of the cases being diagnosed in previous year and because some cases have been started on empiric treatment because of shortage of lab consumables

Table 3: Notification and enrolment of DR-TB cases in 2017

Drug-resistant TB care, 2017	New cases	Previously treated cases	Total number***
Estimated MDR/RR-TB cases among notified pulmonary TB cases			4 100 (2 300–5 800)
Estimated % of TB cases with MDR/RR-TB	2.2% (0.82–4.2)	16% (9.1–25)	
% notified tested for rifampicin resistance		14%	2 116
MDR/RR-TB cases tested for resistance to second-line drugs			0
Laboratory-confirmed cases		MDR/RR-TB: 1 515, XDR-TB: 0	
Patients started on treatment ****		MDR/RR-TB: 1 732, XDR-TB: 19	

Recommendation

- Reconciliation of enrolment figures for the year 2015 may be undertaken and corrected figures reported to WHO
- Expedite activities to cover the remaining 12th province under RR/MDR-TB management services

C. Role of partners in delivery of TB and MDR-TB care

In addition to UN agencies and GDF, the GF, EBF and Christian Friends of Korea (CFK) have been important partners in establishment and roll-out of services. Coverage support provided by GF and EBF has been enlisted in first section. CFK provided support in strengthening the national reference laboratory (NRL) and some other laboratories as well as support for treatment services in some of the provinces.

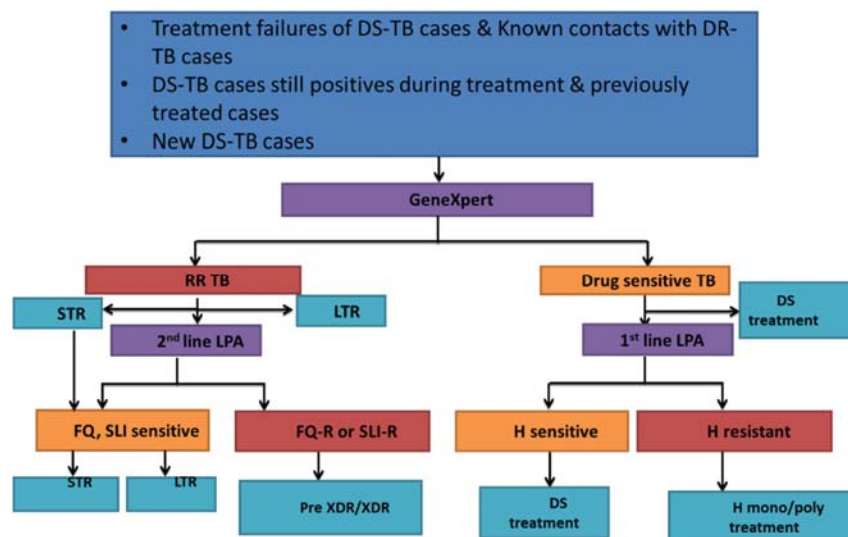
Recommendations

- Till such time Global Fund support is restored or an alternate funding support mechanism is established, the ongoing support from existing partners may need to be enhanced to at least sustain the services in country, if not expand them further

D. Case finding strategy

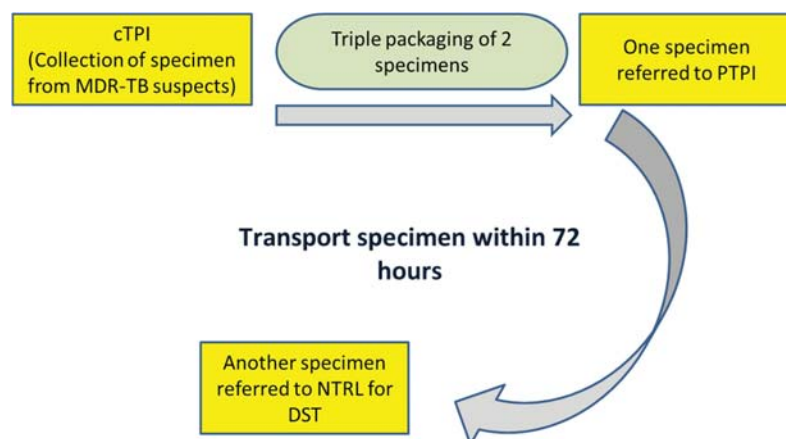
The country is in the process of moving towards Universal DST and there is an in-principle agreement within NTP for the same. As a first step all high-risk symptomatics and new TB cases have been included in the algorithm for screening through GeneXpert. However insufficient cartridge availability makes the use of this algorithm difficult

Figure 4: Algorithm for diagnosis of resistance



Further, a flow chart for sputum transportation to Provincial TB Preventive Institute (PTPI) for GeneXpert testing as well as transport to national reference laboratory have also been finalised

Figure 5: Sputum transportation for DST



Recommendations

- The country should move to universal DST as soon as the cartridges required are available (further discussed in next section)

E. Laboratory services

The national TB reference laboratory (NTRL) is located at Pyongyang. NTRL can potentially perform C&DST, LPA and GeneXpert tests if necessary consumables are available. Regional reference laboratories (RRL) with culture and DST facilities are located in South Hamgyong and North Hwanghae Province. There are 8 GeneXpert machines available with the national TB programme

Table 4: Distribution of 8 GeneXpert machines in the country that belong to NTP

1	Pyongyang city	both	1
2	South Pyongan Province	MoPH/EBF	1
3	North Pyongan Province	MoPH/EBF	1
4	Jagang Province	not covered	
5	South Hwanghae Province	MoPH/EBF	1
6	North Hwanghae Province	MoPH/EBF	1
7	Kwangwon Province	MoPH/GF	1
8	South Hamgyong Province	MoPH/GF	1

9	North Hamgyong Province	MoPH/GF	1
10	Ryangang Province	MoPH/GF	
11	Nampho city	MoPH/EBF	
12	Rason City	MoPH/GF	

Additionally, there are 10 GeneXpert machines used by EBF. However, these machines are for exclusive use by the foundation and not available to NTP for programmatic use.

Calculations for laboratory consumable indicate the following requirements

GeneXpert cartridges using existing algorithm for Treatment failures of DS-TB cases & Known contacts with DR-TB cases; DS-TB cases still positives during treatment & previously treated cases; New DS-TB cases

TOTAL – Approx 120,000 every year

GeneXpert machines

If 8 tests are conducted per machine per day, and 200 days working in year, there is a need for at least **75 machines in total**.

Culture for follow-up of MDR-TB cases and other reasons needs 20,000 test /year while DST

- For first line drugs – 50,000 tests/year
- For second line drugs - 4,000 tests/year

LPA kits corresponding to DST needs (assuming 80 tests/ kit)

- First line: 600 kits/year
- Second line: 50 kits/year

The current situation in country is that

- GeneXpert cartridges – only 4000 available
- Culture for diagnosis and follow-up – sufficient order till Q3 2019*
- DST – sufficient order till Q3 2019*
- LPA – (NA)

Recommendations

Given the scarcity of cartridges and uncertain future, adoption of priority approach for GeneXpert cartridge use (for 4,000 cartridges) + 1000 from EBF is recommended. For the identified categories

- Contacts of MDR-TB
 - Symptomatic and TB by microscopy – direct start on SLD without GeneXpert use

- Symptomatic and no TB by microscopy – evaluate with CxR for need of GeneXpert
 - Asymptomatic and CxR abnormal – GeneXpert
- Treatment failure – use GeneXpert
- Children for TB diagnosis
 - Appropriate sample is available – GeneXpert
 - Sample not available but history of contact, weight loss and/or symptoms, and CxR should guide
- Other high-risk cases for drug resistance
 - Chest X-ray followed by GeneXpert, if needed

However, this is an interim measure only till the situation of cartridges improves. In case upto 20,000 cartridges can be made available then all previously treated cases and non-converters with CxR abnormality or sputum production should be screened.

If 100,000 or more cartridges are available, then all cases starting on TB treatment should undergo GeneXpert testing, if not already done.

Other recommendations

- Upgrade the capacity of RRL laboratory at Hamhung to perform DST along with culture in solid media and LPA.
- WHO and partners to support MoPH to pursue import of LPA test kits from Hain. If this doesn't materialize then alternate options may be explored.
- Partners to work on streamlining import process for available funding – logistics handling agent experienced in this area.

F. Treatment strategy

All laboratory confirmed MDR/RR-TB patients are hospitalized for the complete duration of treatment. Patients are provided MDR-TB treatment free of cost, follow up cultures, nutritional support, wages protection and counseling to the patients. List of MDR-TB presumptive TB cases is available at county level. The NTRL/ PTPI staff collect specimen for GeneXpert and/or C&DST in the field

Current regimen:

- Intensive phase: 8 months Z-Am-Lfx-Eto-Cs (\pm PAS)
- Continuation phase: 10 months Z-Lfx-Eto-Cs (\pm PAS)

As per the updated classification of TB drugs, only 2 Group A and B drugs are being used in longer regimen. Hence the regimen needs strengthening with more effective drugs.

DPR Korea also has a site participating in shorter regimen pilots consisting of Bdq+Dlm+Lzd+Lfx. As per the discussions with the Clinical Programme Director, the initial results of treatment are good,

and the regimen is being well tolerated by the patients. Formal publication of results is yet to be seen.

Table 5: The current situation of drug availability is as under

Drugs	Total Number of patients	Q3 2018	Q4 2018	Q1 2019	Q2 2019	Q3 2019	Q4 2019
Second line drug (SLD) for MDR cases	1000	500 patients put on treatment	Through GF savings for 500 MDR TB patients – in port.	In pipeline, proposed under CERF grant with ancillary drugs			Not available yet

As on dates of the mission, the total enrolled RR/MDR-TB cases by Q2 2018: 947– 500 in MoPH/GF area and 447 in MoPH/EBF area. Given the availability of drugs and pipelines, maximum number of patients who can be initiated on treatment in MoPH/GF area in 2018 is 1000 while MoPH/EBF could potentially provide ~1200 patient treatments. Overall this may lead to shortfall in achievement of enrollment targets in year 2018

Patient interview

The interviewed patients were aware of the disease condition and treatment needs. As of now the patients were receiving treatment as per guidelines and being in the ‘sanatorium’ had received social support as per national guidelines. The patients were confident that treatment will cure them. However, the family members had apparently not been screened so far for TB/DR-TB

Recommendations

- Transition to longer all-oral regimen in all provinces. A guideline development and transition planning group of all stakeholders be formed that should meet within Q1 of 2019. Although the order for longer regimen would have already been placed by then, it may be possible to modify the second tranche of drugs in accordance with latest recommendations.
- Attempt to access free bedaquiline through GDF. It is learnt that EBF is accessing the drug for End TB project. Same channels could be sued for getting additional drugs for programmatic use.
- Standard shorter regimen – if being used should immediately change from use of Kanamycin to Amikacin. Additionally, sites implementing shorter regimen will need
 - SL LPA test for quick decision
 - Audiometry for monitoring adverse events to injectable agent
- Phase out use of Cat II asap with stoppage of procurement of Streptomycin for first line regimen and no further purchase of intermittent regimen for CP

G. Pharmacovigilance/ aDSM

Active drug safety monitoring and management (aDSM) is important for all patients on second-line treatment specifically considering new guidance on RR/MDR-TB management. While the country has made some progress in monitoring and management of adverse events, as of now there is

mostly clinical monitoring of adverse events. Some of the adverse events monitored at the Pyongyang city TB Preventive Institute (CTPI) show the extent of events faced by the patients. The picture is worrisome specifically in absence of adequate means to address these problems

Table 6: Clinically monitored adverse events at Pyongyang CTPI

Side effect	Number of patients with side effects	Percentage of patients with side effects (%)	Onset of symptoms (days)
Nausea and vomiting	28	60.9	145
Joint pain	23	50.0	157
Diarrhea	21	45.7	136
Dizziness	18	39.1	128
Headache	17	37.0	116
Insomnia	16	34.8	98
Abdominal pain	14	30.4	146
Skin rash	8	17.4	135
Appetite loss	9	19.6	98
Depression	6	13.0	68
Mental disorder	3	6.5	8
Hearing loss	21	45.7	156
Visual disorder	10	21.7	87
Kidney disorder	3	6.5	34

There are some test machines available across the country, but reagents are a challenge and hence monitoring tests are not being universally conducted. Haematology and Biochemistry reagents have been ordered but not yet received in the country. There are expected to be sufficient for two quarters. There is also additional possibility for ordering these reagents under the CERF grant. As per the available information 7 'kits' available in EBF areas (ECG, Audiometry, Ishihara charts). In the ex-GF supported areas, monitoring tools are not available at the NTP facility and hence patients need to be referred to General Hospitals in the area to get those tests done.

Table 7: Distribution of tools for adverse events monitoring

	Pyongyang and CTPI	MoPH/GF* (5 areas)	MoPH/ EBF (5 areas)
Complete blood count	2	5	5
CxR	3	5	5
Electrolytes	4	0	5
Electrocardiogram (ECG)	4	0	5
Audiometry	4	0	5
Liver Function Test (LFT)	4	0	5
Thyroid-Stimulating Hormones (TSH)	0	0	0

*These facilities do not have the monitoring facilities within the NTP and patients are apparently referred to general hospital for such tests

Recommendations

- Need for Haematology, Biochemistry analysers and ECG machines at least at the 6 provincial level NTP facilities
- Audiometry will be needed in all provinces using injectables
- TSH measurement needed in all provinces
- 11 digital X-ray machines are reportedly available in the country. There is a need for at least 2 more – for TB and MDR-TB.
- aDSM training for staff at sub-national level – both for clinical management and R&R.
- EBF support in treatment monitoring in additional provinces.

H. Infection control

The mission team observed that personal protective equipment like N95 masks were available and being used at EBF supported facility where patients were being hospitalized. However, MDR-TB patients are being hospitalised for long duration putting strain on the available infrastructure. There was crowding inside the sanatorium wards with 3 female patients together in a small room with insufficient ventilation because of extreme weather conditions. Possibilities of cross infection at such places are high

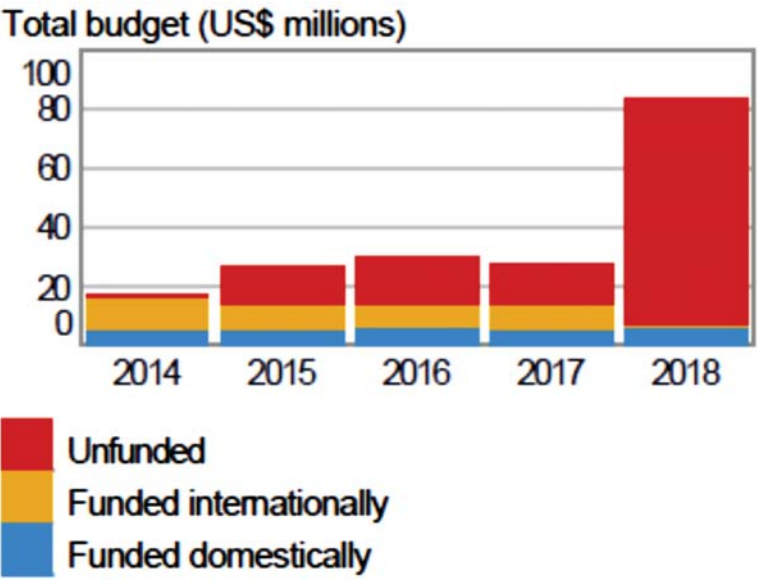
Recommendations

- Reduce hospitalization to minimum possible
- Innovative mechanical ventilation methods maybe explored
- Reduce number of patients in each room. Ideally room of the size should have no more than 1 patient to prevent cross-infection

I. Funding situation for TB programme

The current domestic funding for TB control is close to USD 6 million. As reported to WHO there was a funding gap of USD 70 million for the national programme. This is because of the ambitious plans of country to expand TB and MDR-TB services. As per the original NSP, the funding gap was more than USD 40 million. Either way, unavailability of additional funding is likely to impact the national programme severely.

Figure 6: Trend of funding for the TB programme



Recommendations

- Increased domestic resource allocation for TB control
- Explore additional international funding sources

Schedule of the rGLC mission

Date	Time	Programme	Venue
23 Oct Tue	16:05	Arrival at Pyongyang Accommodation	
24 Oct, Wed	9:00-10:00	Briefing with WR	WHO office
	10:30-12:00	Office work	
	14:00-15:00	Visit TPI, Pyongyang City	PTPI
	16:00-17:30	Visit Treatment Department, Sosong District TPI	Sosong D. TPI
25 Oct, Thu	9:30-12:00	Briefing & Workshop on updated WHO DR-TB guidelines, discussion on GDF mission recommendations, discussions on End-TB project using modified shorter regimen	CTPI
	14:00-17:00		
26 Oct, Fri	9:30-12:00	Office work	WHO office
	14:30-16:30	Meeting with UNICEF	UNICEF/WHO office
27 Oct, Sat		Desk work	
28 Oct, Sun	10.00 – 12.00	Meeting with EBF	
29 Oct, Mon	10:00-12:00	Debriefing with MoPH	Meeting room,
	14:00-17:00	Debriefing with WR Office work	PMU office WHO office
30 Oct, Tue	9:00	Departure from Pyongyang	