



# OUT OF STEP 2015

## TB POLICIES IN 24 COUNTRIES

A survey of diagnostic and treatment practices



# ABOUT MÉDECINS SANS FRONTIÈRES

Médecins Sans Frontières (MSF) is an independent international medical humanitarian organization that delivers medical care to people affected by armed conflicts, epidemics, natural disasters and exclusion from healthcare. Founded in 1971, MSF has operations in over 60 countries today.

MSF has been involved in TB care for 30 years, often working alongside national health authorities to treat patients in a wide variety of settings, including chronic conflict zones, urban slums, prisons, refugee camps and rural areas. MSF's first programmes to treat multidrug-resistant TB opened in 1999, and the organization is now one of the largest NGO treatment providers for drug-resistant TB. In 2014, the organization started 21,500 patients on first-line TB treatment across projects in more than 20 countries, including 1,800 patients with drug-resistant TB.

## ABOUT THE MSF ACCESS CAMPAIGN

In 1999, on the heels of MSF being awarded the Nobel Peace Prize – and largely in response to the inequalities surrounding access to HIV/AIDS treatment between rich and poor countries – MSF launched the Access Campaign. Its sole purpose has been to push for access to, and the development of, life-saving and life-prolonging medicines, diagnostics and vaccines for patients in MSF programmes and beyond.

# ABOUT STOP TB PARTNERSHIP

The Stop TB Partnership is leading the way to a world without TB, a disease that is curable but still kills three people every minute. Founded in 2001, the Partnership's mission is to serve every person who is vulnerable to TB and to ensure that high-quality treatment is available to all who need it.

The Stop TB Partnership's programmes include the Global Drug Facility, which provides quality-assured and affordable TB medicines to countries around the world, and TB REACH, which has helped treat over 1 million people with TB by providing small grants to identify and scale up innovative approaches to TB.

Together our 1400 partners are a collective force that is transforming the fight against TB in more than 100 countries. They include international and technical organizations, government programmes, research and funding agencies, foundations, NGOs, civil society and community groups, and the private sector.

Stop TB Partnership operates through a secretariat hosted by UNOPS in Geneva, Switzerland, and is governed by a Coordinating Board that sets strategic direction for the global fight against TB.

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November 2015





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# **EXECUTIVE SUMMARY**

## Optimized TB Policies: Crucial Steps to Ending TB

This year marks a crucial crossroads in the fight against tuberculosis, which is now the leading global cause of death from an infectious disease. While the Millennium Development Goal (MDG) target to halt and reverse the spread of TB by 2015 was met, there were still 9.6 million new cases and 1.5 million deaths from TB in 2014. This year, world leaders set the most ambitious TB goals yet with the endorsement of the Sustainable Development Goals (SDGs). The SDG target to end TB by 2030, along with the globally-endorsed milestones and targets laid out in the World Health Organization's (WHO) End TB Strategy, together present both a challenge and an opportunity for the TB community to change, adapt, and take every step necessary to realize the vision of a world where no one dies from a disease that is curable and preventable.

At the current rate of progress, the world won't reach the 2030 targets for TB incidence and death until 2182, nearly 150 years behind schedule. The Stop TB Partnership's Global Plan to End TB 2016-2020 sets out to change this through a costed, scalable blueprint for how national TB programmes can become significantly more ambitious and effective over the next five years to meet the 2035 targets in support of the WHO End TB strategy. This will only be possible through a paradigm shift in how we prevent and treat TB, coupled with optimal use of every tool available, forcefully pursued by all stakeholders. How quickly and effectively these tools will be leveraged to boost the TB response is largely dependent upon three factors: effective policies at the national level; full implementation of the latest WHO guidelines; and access to the most effective drugs and diagnostics.

Our survey results illustrate that the global TB response is indeed out of step with known best practices that are essential to meeting the target of a 90% reduction in TB incidence and 95% reduction in TB mortality by 2035. In order to achieve this long-term goal, significant improvements must be made at the national level. These include an enabling policy framework, and an upgrade in tools, strategies, and guidelines in line with international recommendations by WHO. The global TB community also needs a set of metrics, beyond the number of people diagnosed and cured, to monitor progress towards the goals and to help shape demands for the accountability of national governments and global health actors.

## Out of Step Report: A Survey of TB Policies in 24 Countries

Médecins Sans Frontières (MSF) published the first Out of Step Report in 2014 with an assessment of the uptake of TB tools and the status of national TB policies in eight countries. The report identified five deadly gaps in areas of TB diagnosis, treatment of drug-resistant TB, models of TB care, access to new and repurposed drugs, and funding. The survey revealed that countries need to improve their TB policies and take bold steps in order to bend the curve of the TB epidemic downward. It found that the lagging implementation of many policies is indicative of the challenges faced globally by low- and middle-income countries in implementing and funding all of the various components required for a comprehensive and effective TB programme.

The 2015 Out of Step report presents the results of a survey of 24 countries conducted by Stop TB Partnership and MSF. Building on the previous Out of Step report, this year's survey tracked adoption of the latest TB policies, guidelines and tools across five areas: diagnosis and drug resistance testing; drug-sensitive TB (DS-TB) treatment regimens; MDR-TB treatment regimens; models of care; and regulatory frameworks. The results of this survey provide a snapshot of the world's readiness to defeat the TB epidemic. Although effectively implemented policies and guidelines alone will not be sufficient, they form the foundation for a strong and comprehensive TB response that leaves no one with TB behind.

While this report is not a comprehensive or authoritative assessment of countries' national TB policies, it provides an indication of the level of preparedness to implement and scale up action. The results of the survey show that many countries need to take bold steps to bring their policies up to date with the latest international standards. There is a greater need to use rapid molecular tests for diagnosis of TB and drug resistance and to reduce out-of-pocket expenses for people with TB. This, coupled with innovative approaches to active case finding, will help reach the nearly 4 million with TB missed by health systems each year. Older treatment regimens need to be replaced with up-to-date fixed dose combinations for

the treatment of people with TB. People with drug-resistant TB should have access to the most effective drugs and regimens, and many countries need to change their policies to make new drugs available through compassionate use while drugs are being registered and to establish accelerated mechanisms for the registration of new drugs. Updating National Essential Medicines Lists in line with the latest WHO recommendations is also a key step.

While the overall progress towards global TB goals is clearly “out of step”, many countries are making rapid progress towards being in-step with the latest international recommendations. The new Sustainable Development Goal to end TB by 2030 and the Global Plan to End TB 2016-2020 will further challenge countries to ensure that their policies are up to date. We recognize that the adoption and adaptation of policies to national and local situations is challenging and can take time. The countries that participated in our survey are making impressive efforts to put the latest recommended policies in place, and we are grateful for their participation and transparency, which will help inform other countries and serve as a valuable tool for further discussion and learning.

The decisions made at this critical juncture for the TB community will set us on the path to either win or lose the race to reduce TB incidence by 90% and TB mortality by 95 %. Will we continue down the same path, using outdated policies and approaches that have resulted in slow declines over the last 10 years? Or will we step up to the challenge and make this the year that we embrace new tools and innovations in the fight against TB?





# METHODOLOGY



### Purpose / problem statement / research question

The survey was primarily designed to assess the status of national policies in relation to the latest WHO recommendations in five key areas: diagnosis, models of care, treatment of drug-sensitive (DS) TB, treatment of drug-resistant (DR) TB, and the regulatory environment for TB drugs. Where possible, we attempted to assess the extent to which diagnostic policies have been successfully implemented, although this could only be done on a qualitative basis. This survey is a follow-up of the study conducted by MSF in 2014. This updated survey has a broader scope to survey more policy areas and expands the number of surveyed countries from 8 to 24.

### Countries included in the survey

Countries were selected for inclusion in the survey based on their epidemiology and burden of TB and TB/HIV coinfection, as well as the presence of an entity that could complete the survey (either an MSF or a Stop TB Partnership member). The countries represent a range of epidemiological settings for TB (high TB/HIV coinfection rates, high MDR-TB burdens), geographical scope and economic status. The 24 countries included are: Armenia, Afghanistan, Belarus, Brazil, Cambodia, China, Democratic Republic of Congo (DRC), Georgia, India, Indonesia, Kenya, Kyrgyzstan, Mozambique, Nigeria, Pakistan, Papua New Guinea (PNG), Russian Federation, South Africa, Swaziland, Tajikistan, Viet Nam, Uzbekistan, Ukraine, and Zimbabwe.

### Data collection and analysis

The survey consisted of a semi-structured questionnaire with five key sections related to TB diagnostics, models of treatment delivery, treatment regimens for DS-TB, treatment regimens for DR-TB, and drug regulatory environments. The questionnaire was sent to the nominated Stop TB partner or MSF representative at the country level in June 2015. Clear guidance on how to conduct the policy review was given, including what could be used as source/reference documents. The representatives conducted the review of the policy documents and national guidance, and returned the survey by mid-July 2015. Guidelines developed by the World Health Organization (WHO) were taken as reference documents for the different areas included in the survey.

Once the completed survey was returned and the source documents were checked by the Stop TB Partnership, the survey was sent to the NTP managers of the responding countries for additional fact checking and data validation. In some countries the normative guidance is still in the process of being updated in line with global recommendations. In such cases, the content and timeline for the updated guidance are noted, if known. This report contains the analysed data provided by MSF projects, Stop TB Partnership members, and NTP managers.

### Limitations/challenges of the study

The inclusion of countries in the study was dependent on the availability of a partner to complete the survey.

For the diagnostic portion of the survey, country-level information related to the number of GeneXpert devices and their placement could not be validated and therefore has been accepted as presented by the NTP managers and partners.

All the country NTPs were contacted for validation of the information but responses from a few of the countries could not be elicited despite follow-up communication and these included the Russian Federation, Belarus, Armenia, Viet Nam, Kyrgyzstan, Uzbekistan, Kenya and Swaziland.

Some of the countries did not provide information for some of the survey areas, as despite the review of source documents and country guidelines, the information could not be found. In such cases, the response was recorded as 'not known'.





# **COUNTRY SNAPSHOTS AND CRITICAL GAPS**



## CRITICAL GAPS

In order to reduce TB incidence and death in line with the ambitious targets set out in the WHO End TB Strategy<sup>1</sup> and The Global Plan to End TB 2016-2020<sup>2</sup>, countries must work towards closing gaps and implementing critical recommendations. Following is a summary of the key findings of the survey:

## DIAGNOSIS

- Eight countries surveyed have revised their national policies to include rapid molecular tests (e.g. Xpert MTB/RIF) as the initial diagnostic test for all adults and children with presumptive TB, replacing sputum smear microscopy (SSM).
- Fourteen countries have recommended the use of rapid molecular-based testing as the initial diagnostic test for people at risk of HIV-associated TB and MDR-TB, in line with the WHO recommendations<sup>3</sup>.
- Only five countries have recommended Xpert MTB/RIF to be used for paediatric TB diagnosis, and only 4 have recommended the use of Xpert MTB/RIF for extra-pulmonary tuberculosis (EPTB) patients.
- Countries need to reduce significant gaps in implementation of these policies, and must plan strategically to invest resources for wider coverage. Although quantifying the progress made in the implementation of diagnostic policies is complex and requires in depth analysis of the lab network, we have considered the number of GeneXpert devices implemented in countries as a proxy indicator for the status of implementation of WHO recommendation on the use of rapid molecular tests as initial test (either for all TB cases or only for high risk groups). We found that fifteen out of twenty-four countries have reported fewer than 50 devices implemented.

## DS-TB TREATMENT REGIMENS

- Six countries still recommend intermittent treatment for DS-TB; with widespread availability of FDCs for daily regimen and the recommendations of the International Standards of TB care, these should be replaced by daily regimen.
- Ten countries are in line with WHO guidance from 2010<sup>4</sup>, and do not recommend empirical use of the Category II regimen for re-treatment cases.
- Most countries are in line with WHO guidance from 2002<sup>5</sup>, and only three countries do not have Fixed Dose Combinations (FDCs) as the preferred formulation.

## DR-TB TREATMENT REGIMENS

- Only three countries have all the medicines in the five groups of TB drugs in their National Essential Medicine and are in line with the Global WHO Model List of Essential Medicines<sup>6</sup>.
- Five countries did not have a single complete group of any of the MDR-TB drugs on their EML.
- Eleven countries have national guidelines on the use of bedaquiline.
- Only four countries have guidance on the use of delamanid – all in the CIS (Commonwealth of Independent States) region.
- 15 countries have made new and repurposed drugs available through compassionate use or other mechanisms.

# OUT OF STEP

## MAP OF THE 24 COUNTRIES SURVEYED

- 1 Afghanistan
- 2 Armenia
- 3 Belarus
- 4 Brazil
- 5 Cambodia
- 6 China
- 7 DRC
- 8 Georgia
- 9 India
- 10 Indonesia
- 11 Kenya
- 12 Kyrgyzstan
- 13 Mozambique
- 14 Nigeria
- 15 Pakistan
- 16 PNG
- 17 Russian Federation
- 18 South Africa
- 19 Swaziland
- 20 Tajikistan
- 21 Ukraine
- 22 Uzbekistan
- 23 Viet Nam
- 24 Zimbabwe





## MODELS OF CARE

- Seventeen countries have decentralized the initiation of DS-TB treatment at the primary health care level.
- In half of the countries, nurses or health workers can initiate DS-TB treatment and in 17 countries, DS-TB treatment can be initiated in facilities providing HIV care.
- Half of the countries surveyed have guidelines in place to allow the initiation of DR-TB treatment at district level.
- Fifteen countries surveyed do not include routine hospitalization as part of their guidance for the treatment of DR-TB. In countries with compulsory hospitalization in their guidance, the duration of hospitalization ranges from two weeks when the treatment is being initiated to longer durations of eight months during the intensive phase of treatment.

## DRUG REGULATORY ENVIRONMENT

- Fifteen countries have the necessary frameworks in place to offer early access to new drugs through compassionate use or equivalent processes.
- In 15 countries, there is a process of accelerated registration of DR-TB drugs, including new TB drugs.
- Countries should adopt quality assurance mechanisms and standards aligned with the WHO recommendations.

## The pivotal role of the BRICS countries (Brazil, Russian Federation, India, China, South Africa)

Brazil, the Russian Federation, India, China and South Africa – the five countries that form the BRICS group – have a combined population of almost 3 billion and a combined GDP of \$16 trillion. The BRICS countries also account for 46% of all cases of TB and 40% of all TB-related mortality.<sup>7</sup> As such, these countries have the power to drastically reduce the global TB burden through joint cooperation and shared approaches.<sup>8</sup>

China and India alone account for almost 40% of the estimated global burden of TB.

South Africa accounts for 30% of the estimated global number of incident cases of TB/HIV coinfection. With regard to multidrug-resistant tuberculosis (MDR-TB), China, India and the Russian Federation together account for more than half – 56% – of the estimated global burden. Brazil accounts for about a third of the western hemisphere's estimated burden of TB and MDR-TB.

## Diagnosis

- South Africa, Brazil and the Russian Federation have recommended rapid molecular testing as the initial diagnostic test for all presumptive TB cases, replacing sputum smear microscopy. However, only South Africa has reached 100% coverage of rapid molecular tests (e.g. Xpert MTB/RIF) in the public sector. In Brazil and the Russian Federation, implementation of this policy is still being scaled up.
- India has recommended the use of rapid molecular tests as the initial test only for people at risk of MDR-TB or HIV-associated TB. However, roll-out has been progressing slowly, despite the establishment of clear and ambitious scale-up plans.
- China has only recommended the use of rapid molecular tests for TB-confirmed cases, with the purpose of testing for drug-resistance. However, authorities have reported that they are in the process of revising their guidelines and will be introducing Rapid Molecular Test as the initial diagnostic test in their new guidelines.

- All the BRICS countries have recommended first-line Drug Susceptibility Testing (DST) (including at least rifampicin and isoniazid) for all groups of patients at risk of MDR-TB and second-line DST for all people with drug-resistant TB.

### DS-TB treatment guidelines

- Category II treatment regimens containing streptomycin are still recommended by India and China despite their high burden of MDR-TB and despite recommendations for DST for those at risk of MDR-TB.
- India and China still recommend intermittent therapy for DS-TB, instead of daily therapy.
- FDCs are still not the recommended formulation for India and Russian Federation.
- All the BRICS countries have updated their paediatric guidance to reflect the new doses of first-line drugs.

### DR-TB treatment guidelines

- Using the national essential medicine list as an indicator for the availability of drugs, the inclusion of all the drugs for Group 2-5 medicines on national essential medicines list (EML). Russia and South Africa include Groups 2,3,4, Brazil includes Group 3, and India includes none.
- Russia, India, and South Africa have national guidelines in place on the use of bedaquiline, while none of the BRICS countries have guidelines in place on the use of delamanid.

### Models of care

- Brazil, India and South Africa have a policy of decentralization of DS-TB treatment initiation at the primary health care level.
- Brazil and South Africa have a policy to allow nurses or health workers to initiate DS-TB treatment.
- A policy for TB treatment initiation in facilities providing HIV care is present in all BRICS countries except for Russian Federation.
- Routine hospitalization of MDR-TB Patients is a policy in India, China and South Africa.

### Drug regulatory environment

- South Africa, Russian Federation and China have an accelerated registration for MDR-TB drugs. South Africa has taken the lead in introducing bolder policies at country level by introducing new TB drugs.
- Four BRICS countries (Brazil, Russian Federation, India and South Africa) have a policy for new and repurposed drugs to be available through Compassionate Use or patient named basis mechanisms.



# THE FIVE KEY STEPS

# I. DIAGNOSIS

## Key findings

- Most of the countries included in the survey have updated their national guidelines for TB diagnosis to be consistent with WHO recommendations<sup>3</sup>, including recommending rapid molecular testing as the initial test for people at risk of MDR-TB and HIV-associated TB (high-risk groups).
- Very few countries have considered recommending rapid molecular testing as the initial test for all presumptive TB cases. Despite the upfront financial challenges related to this strategy, countries should consider expanding access to rapid molecular diagnostics in order to: ensure early diagnosis and early treatment initiation; reduce the chain of transmission; reduce cost implications in the long run; and reduce the emergence of drug-resistant TB cases and the overall global burden of TB.
- At the policy level, the main weakness is the lack of recommendations for the use of rapid molecular testing as the initial diagnostic test for children at risk of MDR-TB or HIV-associated TB and for selected forms of EPTB.
- Despite policies being updated in line with the latest WHO recommendations, countries still need to reduce significant gaps between policy and implementation, and to strategically invest resources to achieve wider coverage. Such actions are needed to reach the targets set out by the WHO End TB Strategy and The Global Plan to End TB.

## Background

Early and accurate diagnosis of TB is key to ensuring a successful TB control programme<sup>9</sup>. Sputum smear microscopy (SSM) and culture, used for decades, have serious limitations when compared to the rapid molecular testing introduced in recent years. While specific results vary, in general SSM is not very sensitive, detecting only about 50% of all active cases of TB, and even fewer among children and people living with HIV; SSM cannot be used to diagnose drug resistance<sup>10</sup>. While culturing is more sensitive than SSM and can be used for drug-susceptibility testing (DST), TB culture requires expensive biosafety facilities, trained laboratory technicians and can take up to several weeks to obtain results.

Rapid molecular tests for TB and drug-resistant TB have the potential to increase the number of MDR-TB cases detected and decrease the turnaround time for results compared to conventional methods<sup>11</sup>. WHO has to date recommended two such tests: the Xpert MTB/RIF assay that runs on the GeneXpert platform (Cepheid) and Line Probe Assays (LPAs). LPAs are suitable for implementation at the reference laboratory level<sup>12</sup>. The most widely implemented LPA (the Hain Life science Genotype MTBDRplus) can detect resistance to rifampicin and isoniazide, the two cornerstone drugs of DS-TB treatment.

Xpert MTB/RIF is the first molecular test that can be used for simultaneous detection of TB and rifampicin resistance and be implemented at the decentralized level (district and sub-district laboratories). WHO recommends Xpert MTB/RIF as the initial diagnostic test for diagnosis of pulmonary TB and rifampicin resistance in people at risk of MDR-TB or HIV-associated TB (high risk groups); in addition, WHO conditionally recommends Xpert MTB/RIF as a follow-up test to SSM in settings where MDR-TB or HIV are of lesser concern, especially for further testing of smear-negative specimens. WHO recommends that Xpert MTB/RIF be used as the initial diagnostic test (replacing SSM) in all cases of presumptive TB, if resources can support this strategy; in addition, WHO recommends Xpert MTB/RIF as the initial test for diagnosis of MDR-TB and HIV-associated TB in children, and for the diagnosis of extrapulmonary TB (with its use being restricted to some selected sample types)<sup>13,14</sup>.

Despite these recent advances, significant gaps remain in the early detection of TB cases and in the implementation of proper diagnostic work-ups for presumptive TB and DR-TB cases. In 2014, just over 6 million of the estimated 9.6 million TB incident cases were notified to national TB programmes (NTPs), leaving about 3.6 million cases undetected (or unreported). The latest WHO data also show that little progress has been achieved in the detection of MDR-TB.

## Xpert MTB/RIF as the initial diagnostic test for persons to be evaluated for TB

The survey results show that only 9 of the 24 countries surveyed (38%) have marched ahead and revised their national policies to include rapid molecular tests (e.g. Xpert MTB/RIF) as the initial diagnostic test for all adults and children with presumptive TB, replacing sputum smear microscopy (SSM).

**Table 1: Status of recommendation of rapid molecular testing by Country**

Countries that recommend rapid molecular tests as the initial test for all presumptive TB cases	Countries that recommend rapid molecular tests as the initial diagnostic tests only for high-risk groups
Belarus	Afghanistan
Brazil* (subnational)	Cambodia
Georgia	DRC
Russian Federation	India
South Africa	Indonesia
Tajikistan* (subnational)	Kenya
Ukraine* (not widely; only at oblast level)	Kyrgyzstan
Swaziland (implemented widely, but with technology stock-outs)	Mozambique
	Nigeria
	Pakistan
	PNG
	Uzbekistan* (subnational)
	Viet Nam
	Zimbabwe

**Note.** Georgia is in the process of updating its guidelines, which are expected to be available towards the end of 2015.

Although eight countries have already revised their policies, the extent of implementation of these policies and the roll-out of rapid molecular testing vary significantly among countries. In seven out of the nine countries that recommend rapid molecular testing as the initial test for all presumptive TB cases (namely, Russian Federation, Belarus, Brazil, Uzbekistan, Ukraine, Tajikistan and Georgia), the policy has been implemented only at the subnational level, and the roll-out has not reached nationwide coverage (see also section "Status of Xpert MTB/RIF roll-out: Policy versus implementation" for more details).

Out of the 24 countries for which data were analysed, 14 countries (namely Uzbekistan, India, Mozambique, Pakistan, Viet Nam, Nigeria, Afghanistan, Cambodia, Democratic Republic of Congo (DRC), Kyrgyzstan, Indonesia, Kenya, Zimbabwe and PNG) have recommended the use of rapid molecular-based testing as the initial diagnostic test for people at risk of HIV-associated TB and MDR-TB, in line with the WHO recommendations. However, based on the feedback received through our survey, the extent of implementation of this policy seems to vary significantly among countries (see Table 3 'Diagnostics Implementation Summary').

In Armenia, SSM remains the initial diagnostic test. However, all people with presumptive TB are tested for drug resistance using rapid molecular tests (sputum smear negative cases are tested by Xpert MTB/RIF, while sputum smear positive cases are tested by LPA)



In China, rapid molecular testing is only recommended for use in confirmed TB cases for the purpose of screening or testing for drug resistance. It was reported that Xpert MTB/RIF testing is recommended for smear-positive patients only.

### Patient categories for which countries recommend Xpert MTB/RIF

High-risk groups (MDR-TB and HIV-associated TB)	Paediatric TB	EPTB	Smear (-)ve
Belarus, India, Mozambique, Pakistan, Viet Nam, Brazil, Afghanistan, Nigeria, Cambodia, DRC, Kyrgyzstan, Uzbekistan (TB/HIV coinfectd), Ukraine, Indonesia, Tajikistan, Kenya, Zimbabwe, PNG, South Africa, Swaziland	India, Viet Nam, Nigeria, Kyrgyzstan, Zimbabwe	India, Pakistan, Viet Nam, Nigeria	Armenia

The survey results show that only 5 out of 24 countries have recommended Xpert MTB/RIF to be used for paediatric TB diagnosis, and only 4 out of 24 countries have recommended the use of Xpert MTB/RIF for EPTB patients. This level of uptake is unsatisfactory.

### Xpert MTB/RIF for testing or screening for the identification of drug resistance

All of the countries included in this study, with the exception of Viet Nam, Kyrgyzstan and Georgia, reported that they recommend rapid molecular testing for the purpose of testing or screening for drug resistance.

## Status of Xpert MTB/RIF roll-out: Policy versus implementation

The number of Xpert MTB/RIF devices implemented in each of the 24 countries varies widely. Fifteen out of twenty-four countries have reported fewer than 50 devices implemented. The number of devices deployed does not match the need and the current epidemiological situation in these countries calls for all high-risk patients to have access to Xpert MTB/RIF testing. The number of Xpert MTB/RIF devices deployed was reported by survey respondents and could not be verified independently from existing sources. The development of population-based indicators (for example, taking into account TB and HIV epidemiology) would greatly support a proper assessment of available capacity of rapid molecular testing and would help verify whether testing capacity is realistically aligned with needs.

## Countries that have recommended Xpert MTB/RIF as the initial diagnostic test for all presumptive TB cases

Among the countries that have adopted this recommendation, there is significant variation in the extent of implementation and the progress made in the roll-out of rapid molecular testing:

- South Africa is at the forefront of Xpert MTB/RIF implementation, having opted for replacing smear microscopy with Xpert MTB/RIF and achieving 100% coverage in the public sector.
- Swaziland reports that it has adopted the policy, but the level of coverage is not reported.
- Brazil and Russian Federation have also shifted towards a diagnostic algorithm that recommends use of Xpert MTB/RIF (or other molecular-based tests in the case of Russian Federation) as the initial diagnostic test for all presumptive TB cases, but implementation is still in progress. Brazil's rapid molecular test network currently covers 55% of TB cases in the country and expansion of this network is being planned.
- In Belarus and Tajikistan rapid molecular tests are recommended as the initial diagnostic test for all presumptive TB cases, but roll-out is progressing slowly (i.e. only 15 Xpert MTB/RIF devices have been reported to be implemented in each country).
- The situation is similar in Ukraine, where Xpert MTB/RIF roll-out has progressed very slowly and where the use of this test as initial diagnostic test for all presumptive TB cases is limited to a few regions only.
- In Georgia the national guidelines are under revision and it is reported that the new guidelines will be published by the end of 2015. For the time being, only 16 devices have been reported to be implemented in the country.

## Countries that have recommended Xpert MTB/RIF only for high-risk groups

Based on survey results, the extent of implementation of this policy varies significantly among countries (see Implementation summary: Qualitative analysis of implementation).

## Placement of Xpert MTB/RIF devices

Seventeen countries provided data on the placement of Xpert MTB/RIF devices. Most of the countries (13 out of 17) reported that the majority of Xpert MTB/RIF devices have been placed at district and subdistrict level or below, in line with the WHO recommendations to enable the decentralization of DR-TB diagnosis. By contrast, most of the devices in Armenia, Viet Nam, China and Indonesia have been placed in central facilities.

**Table 2: Xpert MTB/RIF availability at the country level (based on country feedback)**

List of countries	Reference lab (nr of devices)	Specialized hospital (nr of devices)	District level/ subdistrict level (nr of devices)	Microscopy centre level (nr of devices)	Community outreach or mobile clinics (nr of devices)	Remarks from countries
Afghanistan	● (1)	● (1)				2 machines available (1 in NRL and 1 private hospital)
Armenia	● (2)	● (1)	● (1)	-	-	
Belarus	● (1)	-	● (13)	-	-	Penitentiary /prisons (1)
Brazil	● (5)	● (26)	● (17)	● (126)	● (1)	
Cambodia	● (3)	●	● (23)	-	● (2-4)	
China	●	●	-	-	-	
DRC	● (1)	-	● (11)	● (29)	-	
Georgia	● (4)	-	-	● (10)	-	Penitentiary/Prison (2)
India	● (4 atNRL; 18 atRL)	● (35)	● (62+2)			Plans to cover all districts by end 2017 (950 devices)
Indonesia	● (6)	● (39)	-	-	-	
Kenya	● (1)	● (3)	● (69)	-	-	
Kyrgyzstan	●	●	●	-	-	Sokuluk FMC - 1 CTBD Bishkek - 1 Batken oblast TB centre - 1 Talas oblast TB centre - 1 Osh city TB centre - 1
Mozambique	● (3)	● (2)	● (31)	-	-	
Nigeria	● (2)	-	● (4)	-	-	A total number of 131 devices implemented has been reported but no complete info on placement is available
Pakistan	● (6)	-	● (36)	-	-	
PNG	●	-	●	-	-	And provincial level hospital (Numbers not reported)
Russian Federation	Not known	Not known	Not known	Not known	Not known	
South Africa	Not known	Not known	Not known	Not known	Not known	
Swaziland	-	-	●	-	●	There are also few PPM sites
Tajikistan	● (6)	● (1)	● (8)	-	-	
Ukraine	● (1)		●			NRL: 1 G/Xpert; 3rd Level lab – 29 (28 G/Xperts 4-module device and 1 G/Xpert 1-module device ); 3rd level prison labs 8 (G/Xpert 4-module device in each lab); 2nd level labs - 3 (2 G/Xpert 4-module device, 1 G/Xpert 1 module device). 7 - 1st lab level (AIDS center) G/Xpert 4-module device in each lab. In process of installation 3 G/Xpert 4-module device
Uzbekistan	●	-	●	-	-	Karakalpakstan: 5 - central level, 1 - district. By the end of 2015: 5 - central, 3 - district Tashkent: National AIDS Centers: 2; NRL: 2; Oblast (state level) and Rayon level: 15
Viet Nam	● (6)	● (37)	● (3)	-	-	
Zimbabwe	● (2)	● (13)	● (71)	● (8)	● (2)	5 are at PPM sites which collaborate very well with the NTP and these are counted under district / sub-district level

**Legend:** ● yes

**Note:** number of devices placed at the different levels of the laboratory network are reported in parentheses when this information was made available by countries (status as of August 2015)



## Use of WHO-approved rapid molecular tests for the diagnosis of TB

Countries responded that they are mostly recommending the use of WHO-approved rapid molecular tests in the algorithms for the diagnosis of TB.

### **Drug-susceptibility testing (DST)**

All countries included in the survey reported that their national guidelines recommend first-line DST for all rifampicin-resistant (RR) patients and for all patients considered at risk of MDR-TB.

Seven countries have adopted a more aggressive strategy for detection of MDR-TB cases and recommend first-line DST for all confirmed TB cases: Russia, Belarus, Kyrgyzstan, Ukraine, Tajikistan, Georgia, South Africa

All countries included in the survey reported that their national guidelines recommend second-line DST for all RR, PDR-TB and MDR-TB patients.

However, qualitative feedback from the survey indicates that implementation of first-line and second-line testing policies varies among countries, and access to testing may not be uniformly available. The availability of DST for first-line and second-line drugs is captured and highlighted in the table on the right.

# DIAGNOSTICS IMPLEMENTATION SUMMARY



LEGEND



Not implemented



Fully implemented



Partially implemented

**Disclaimer:** This is purely based on qualitative feedback provided by key informants

## II. DS-TB TREATMENT REGIMENS

### Key findings

- Countries should phase out empirical use of Category II regimens for treatment of TB as rapid diagnostic tests become more widely available.
- Countries must ensure that FDC formulations, which have fewer side effects, are recommended and made available in the country for use.

### Intermittent dosing

WHO recommends daily dosing<sup>4</sup> wherever feasible with a high grade of evidence<sup>15,16</sup>. The recommendations note that intermittent dosing (three times per week), although not ideal, can be used during the continuation phase if each dose is directly observed.

Six out of the twenty-four countries surveyed still use intermittent treatment. Armenia and Kyrgyzstan recommend only for patients with side effects and under special circumstances. In Indonesia, it is recommended during the continuation phase for Category I and Category II treatment. In Ukraine, it is recommended for patients in Categories I-III only during the continuation phase, except in the case of TB/HIV coinfection or paediatric TB. In India and China, intermittent therapy is still recommended.

A recent study in India<sup>17</sup> showed that within the intermittent dosing group there was a higher rate of people lost to follow up from treatment, which carries the associated risk of resistance generation. Although India continues to recommend intermittent dosing, the NTP reported that a daily treatment will be rolled out in 104 districts in 2016, and since March 2015, pilot projects looking at daily regimens have been initiated in 30 high workload ART centres for people coinfecting with TB/HIV. It is important that India's draft policy recommending a daily treatment regimen, prepared in 2014, be approved and implemented soon.

### Category II Treatment

In the 2010 WHO guidelines<sup>4</sup>, it was predicted that the Category II re-treatment regimen would be phased out, especially with the increase in access to rapid diagnostic tests. The guidance stated that the use of rapid DST methods would eventually eliminate the need for a re-treatment regimen (Category II). While this scale up of rapid DST is occurring, WHO recommends Category II treatment in only two circumstances:

- In countries with limited access to rapid DST, Category II treatment is recommended while patients who have relapsed or are returning after treatment non-completion are awaiting DST results (if country-specific data show low or medium levels of MDR-TB in these patients or if such data are not available).
- In countries that do not yet have DST routinely available at the start of treatment for all previously treated patients, the Category II treatment can be used for the duration of treatment on an interim basis until laboratory capacity is available.

As countries revise their diagnostic policies and implement rapid DST, there should be a corresponding decrease in the use of Category II treatment. The target for the 2011-2015 Global TB Plan was to have all previously treated cases receive DST for first-line drugs, but in 2014 only 58% of previously treated cases were tested. The Category II regimen, which adds streptomycin to the DS-TB treatment regimen, has been shown to have poor outcomes in countries with high background rates of MDR-TB and high TB/HIV coinfection rates<sup>7</sup>. Increased levels of streptomycin resistance have been found in China<sup>18</sup> India<sup>19,20</sup> Mozambique<sup>21</sup>, Uzbekistan<sup>22</sup> and Viet Nam<sup>23</sup> where the Category II regimen is still recommended.

Ten of the twenty-four countries in the survey no longer recommend Category II treatment. Of the remaining 14 that continue to recommend and use Category II treatment, 10 of them are among the top 22 high-burden TB countries and three have a high HIV burden. With continued scale up in access to rapid diagnostic testing in all these countries, Category II treatment should be removed from the TB treatment guidelines. DST must be offered as a priority to all re-treatment and high-risk cases in order to ensure that the correct treatment is provided from the very beginning.

### Fixed-dose combinations (FDC)

The 2010 WHO guidelines recommend fixed-dose combinations for the treatment of DS-TB. FDCs simplify the treatment regimen for patients, causing fewer side effects and reducing the pill burden<sup>24</sup>. Although mono-substances are available, they present more challenges for dosing, procurement and logistics.

Only three countries (India, Russian Federation and Ukraine) do not have FDCs as the preferred formulations in their guidelines. The Russian Federation and Ukraine recommend mono-substances as the formulations for the treatment of DS-TB. The Standards for TB Care in India (STCI)<sup>25</sup> state that “fixed dose combinations (FDCs) are desirable as they simplify drug procurement and logistics, the delivery of DOT and may increase adherence... It was recommended that the programme undertake operational research to assess the feasibility of implementing daily therapy using FDCs under direct observation under programmatic settings”. These recommendations have yet to translate into national guidelines.

There are a number of different FDCs on the market, and it is important that the FDCs available and recommended conform to the WHO dosing and quality recommendations. FDCs are particularly important for the treatment of children with DS-TB. The doses for first-line drugs (FLD) for children were increased in 2010 and further updates were made in the latest WHO paediatric TB guidelines<sup>26</sup>. The good news is that five years following the interim recommendation on the paediatric FLD dosages, only three countries (Swaziland, Viet Nam and Ukraine; the status of Viet Nam and Ukraine are not known) have yet to update their guidance on the doses required for the FLD treatment of children. While new FDC products that reflect these increased dosages are being developed, there are interim recommendations regarding how to dose children using the existing FDC products. The new FDC products are expected to be released by the end of 2015. It is important that countries update their dosing tables so that these new products can be quickly and easily implemented by treatment providers.

In addition to updating the doses required for the treatment of DS-TB in children, the WHO recently reviewed and updated all areas of the treatment of paediatric TB in its 2014 guidance. Seven countries updated their guidance in 2014 (namely, India, Belarus, Mozambique, Pakistan, Uzbekistan, Tajikistan and Georgia), and Brazil is currently in the process of updating its guidance. This timely updating of national policies following the release of new and updated WHO guidance is what is required and should be the normative process for all policy updates.

## III. DR-TB TREATMENT REGIMENS

### Key findings

- Countries should regularly update National Essential Medicine Lists to be in line with the Global WHO Essential Medicine list.
- Drugs categorized as “Group 5” should be made available for patients with complex forms of drug-resistant TB.
- Compassionate use or other similar mechanisms should be established to ensure access to new drugs while the programmatic use of the drugs is being planned.

Treatment recommendations for MDR-TB currently involve an individualized approach that compiles a regimen using drugs that the patient is sensitive to from the five groups or classes of drugs.

#### TB drugs used to treat drug-resistant TB according to group (class)

Classification of TB Drugs	Drugs included in this category
Group 1	pyrazinamide, ethambutol, rifabutin, isoniazid, rifampicin, rifapentin
Group 2	kanamycin, amikacin, capreomycin, streptomycin
Group 3	levofloxacin, moxifloxacin, ofloxacin
Group 4	para-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide
Group 5	bedaquiline, delamanid, clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid, clarithromycin,

It is important that treatment providers have access to all drugs in each group so they can construct the best possible regimen for the patient. Adding these drugs to National Essential Medicines Lists (EML) is one key way to make these drugs more easily accessible. The WHO EML – a list of the most efficacious, safe and cost-effective medicines for priority conditions that in total represents the minimum medicine needs for a basic health care system – can guide countries in the development of their national EML. Drugs on the EML have also been evaluated for cost-effectiveness against other alternatives in the same class of medicines. The WHO EML is updated every two years by an expert committee made up of recognized specialists from academia, research, and the medical and pharmaceutical professions.

In 2015, WHO added five TB drugs to the EML: bedaquiline, delamanid, linezolid, rifapentine and terizidone<sup>27</sup>. Only three of the 24 countries have all the medicines in all five groups on their national EML lists (Cambodia, Belarus and Ukraine). The availability of group 5 drugs on the EML was the weakest with the remaining countries having no or few of the group 5 drugs on their EML. For the remaining groups of drugs, five countries had just one complete group of drugs on their national EML, four countries had just two complete groups, and five countries had three complete groups. Five countries (India, Nigeria, Kyrgyzstan, Kenya and Zimbabwe) did not have a single complete group of any of the MDR-TB drugs on their EML. Group 4 has two drugs from the same class with equivalent efficacy (prothionamide/ethionamide and cycloserine/terizidone). For countries that have only one of the drugs from that class on their EML, the survey results have been highlighted to reflect this.

### New drugs for the treatment of DR-TB

For the first time in nearly 50 years, two new compounds – bedaquiline and delamanid – have been conditionally approved for the treatment of MDR-TB in cases where an effective treatment regimen is not otherwise available. Bedaquiline (Janssen), the first new drug, received accelerated approval from the US Food and Drug Administration (FDA) in December 2012<sup>28</sup>. The second drug, delamanid (Otsuka), received approval from the European Medicines Agency (EMA) and Japan's Pharmaceuticals Medical Devices Agency (PMDA) in 2014<sup>29</sup>. Alongside these completely new drugs, there is growing evidence on the potential role of repurposed medicines, including clofazimine and linezolid, which are showing effectiveness against drug-resistant forms of TB<sup>30,31,32</sup>.

In addition to ensuring that these new medicines are on the EML (in line with the recent 2015 update of the EML), countries also need to issue national guidance on their use. Eleven countries have national guidelines on the use of bedaquiline. There are additional three countries using bedaquiline in pilots or compassionate use programmes (in India, Pakistan and Uzbekistan) that have issued interim guidance for the use of bedaquiline in these settings.

Only four countries have guidance on the use of delamanid – all in the CIS (Commonwealth of Independent States) region (i.e. Belarus, Kyrgyzstan, Tajikistan and Georgia). Two of these countries (Belarus and Georgia) have access to delamanid through compassionate use programmes. Armenia has guidance on the use of delamanid but this has yet to be incorporated into national guidelines.

## Compassionate use

Compassionate use refers to the use of an investigational drug outside of a clinical trial by patients with serious or life-threatening conditions who do not meet the enrolment criteria for the clinical trial in progress. Compassionate use has been used as an interim solution for accessing bedaquiline and delamanid for patients with XDR-TB or failing on MDR-TB regimens. Fifteen countries have the necessary frameworks in place to offer early access to new drugs through compassionate use or equivalent processes. Although the compassionate use programme for bedaquiline is coming to an end as the programmatic use of this drug is scaled up via the USAID donation programme, it remains important that countries consider putting in place the necessary framework to allow access to other drugs yet to be registered to be used for the treatment of complex MDR-TB cases, for example, delamanid and pretomanid (also known as pa-824). Compassionate use programmes offer earlier access for patients who need new drugs and the benefit of clinical experience using the new drug, but compassionate use is not a long term solution; planning for the larger programmatic introduction of new drugs should happen in parallel.

## IV. MODELS OF CARE

### Key findings

- Decentralization of all aspects of TB care can and should be implemented; this patient-focused model does not affect outcomes and has positive cost implications.
- Routine hospitalization for any type of TB is not needed.
- Nurse-initiated treatment for DS-TB can be considered and is being used in some countries.
- Integration of TB and HIV treatment needs to be prioritized: how and where people receive treatment is important.



## Models of care for DS-TB

Treatment for TB is a considerable burden for patients, requiring a minimum of six months of treatment with multiple, if not daily, visits to health care services<sup>33</sup>. In order to improve adherence, infection control and ensure the minimal disruption to patients, TB services should be decentralized as much as possible, especially for DS-TB. Evidence has shown that moving treatment centres closer to the patient results in decreased costs to the patient, as well as decreased costs to the programme<sup>34,35,36</sup>. Seventeen out of twenty-four of the countries in the survey had DS-TB treatment starting at the primary health care (PHC) level. In addition to moving services closer to the patient, a further step in the decentralization of DS-TB care is to allow nurses to initiate treatment. This approach has been formalized in the treatment of HIV, where task shifting (i.e. the delegation of tasks performed by physicians to staff with lower-level qualifications) is considered a crucial means of expanding access to treatment in resource-poor settings or settings with limited medical human resources and has seen no change in outcomes<sup>37</sup>. The challenges regarding health care worker (HCW) shortages are also present for TB<sup>38</sup>, and task shifting should be considered an option in settings with limited resources. Half of the countries surveyed allowed nurses or health care workers to initiate DS-TB treatment. All of the Africa region countries included in this survey allow for HCW-initiated treatment. This may be due to these countries' experience with using this model for their HIV services. Furthermore, countries with a policy regarding HCW-initiated treatment for DS-TB also reported a complementary policy on the PHC-level initiation of treatment. This approach enables positive steps towards the full decentralization of DS-TB services and all the benefits that confers on patients.

### **Countries where nurses/HCWs can start adults on DS-TB treatment:**

Mozambique, Viet Nam, Brazil, Nigeria, Cambodia (for smear + cases), DRC, Georgia, Kenya, Zimbabwe, PNG, South Africa, Swaziland

The status of initiation of TB treatment in other countries is highlighted in the table below.

**Table 4:** Status of initiation of DS-TB treatment

Countries where nurses do not initiate TB treatment	Who initiates DS-TB treatment ?
Afghanistan	Only relevant doctors can initiate treatment for DS-TB
Armenia	Nurses are only responsible for implementation of DOT
Belarus	Not specified
Georgia	Only after prescription from TB doctor
China	Not specified
India	Physician
Indonesia	Not specified
Kyrgyzstan	Only TB specialists can initiate treatment following Consilium decision
Pakistan	Not specified
Russian Federation	Only TB doctors
Tajikistan	Only TB doctors can initiate treatment after confirmation of TB Council
Ukraine	Not specified
Uzbekistan	Not specified

The following is the situation in countries that do not recommend the initiation of DS-TB at the PHC level.

**Table 5:** Initiation level of treatment for DS-TB

Country	Who initiates DS-TB treatment ?
Russian Federation	After decision of central region TB medical committee
Belarus	Status not known
China	Country level (reported by NTP response)
Kyrgyzstan	Status not known
Uzbekistan	TB treatment is initiated at the district / rayon level.
Ukraine	According to Order No. 620 (Consolidated TB protocol), patients with extrapulmonary tuberculosis with positive sputum smear by bacterioscopy method have to be hospitalized (in exceptional cases patients with bacteria excretion by smear can be treated at home if conditions for infection control have been provided). Under the regulatory framework, patients may be treated in institutions that provide primary health care. However, institutions of primary health care are not involved in the proper management of patients with TB.
Georgia	Only case detection and referral to a regional TB facility are done at the PHC level. After diagnosis is confirmed and the patient is registered at the TB facility, PHC nurses can give TB treatment prescribed by a TB doctor.

## Models of care for DR-TB

The treatment for MDR-TB is long, complex and expensive with poor outcomes and high rates of people lost to follow up. Two of the main variables contributing up to 90% of the costs of a DR-TB regimen are drugs and hospitalization<sup>39</sup>. WHO has recommended ambulatory models of care<sup>40</sup>, and decentralization of DR-TB services could have significant impact on the total cost of treating MDR-TB. Decentralization has not been associated with poorer outcomes<sup>41,42,43</sup>, and is associated with decreased rates of people lost to follow up<sup>44</sup> and lower costs.<sup>45,46,47</sup>

The process of decentralizing DR-TB services is not as straightforward as for DS-TB, as DR-TB patients may be more likely to require hospitalization due to the likelihood of the patient being sicker and the complexities and side effects of the treatment. Despite this difficulty, it is important that hospitalization only be recommended based on the clinical condition of the patient and not routinely recommended or made compulsory. Treatment initiation can still be decentralized to at least the district level. Half of the countries surveyed have guidelines in place to allow the initiation of DR-TB treatment at district level. In five countries in the CIS (Russian Federation, Armenia, Georgia, Uzbekistan and Tajikistan), TB treatment decisions are determined by a TB committee that also decides the level at which DR-TB treatment can be started.

However, Armenia has policies that recommend compulsory hospitalization for DR-TB patients, thus weakening the potential advantages of decentralizing treatment initiation. More than half of the countries surveyed do not include routine hospitalization as part of their guidance for the treatment of DR-TB. In countries with compulsory hospitalization in their guidance, the duration of hospitalization ranges from two weeks when the treatment is being initiated to longer durations of eight months during the intensive phase of treatment. This places a large burden on both the patient and the national TB programme with regard to the cost and infection control issues<sup>48</sup> associated with hospitalization. (Please refer to Table 6 for the duration of hospitalizations.)

There have been two policy changes among the countries reviewed in the 2014 Out of Step report. The Russian Federation previously had a policy of hospitalizing all forms of TB until smear conversion or for eight weeks, whichever happened first. It changed this policy at the end of 2014 (Order of MOH RF #951 from 29/12/2014) and routine hospitalization is no longer required for the intensive phase of DS-TB. The decision to hospitalize now lies with the TB Committee, based on the individual situation of the patient. Uzbekistan changed its policy at the end of 2014, removing compulsory hospitalization for DR-TB (although this was not required for DS-TB patients). This policy shift away from routine hospitalization is to be welcomed; the next step is ensuring that these policies are implemented. Cost savings resulting from

this policy change should be reinvested in the national TB programme in order to ensure that all patients who need treatment can access it, and that the programme can build its capacity towards the further decentralization of TB care.

**Countries that DO NOT RECOMMEND routine hospitalization for the treatment of DR-TB (15/24)**

Brazil, PNG, Russian Federation\*, Mozambique, Pakistan, Nigeria, Cambodia\*, DRC, Uzbekistan\*, Ukraine, Indonesia, Kenya, Zimbabwe, Swaziland, Tajikistan

\*Russian Federation: depends on the individual patient's situation (Order of MOH RF #951 from 29/12/2014);  
Cambodia: initial few days may be required to check the tolerance of drugs; Uzbekistan: Prikaz No 383, MOH (24 October 2014)

**Table 6: Duration of hospitalization for DR-TB treatment**

Country	Duration of hospitalization
India	Approximately 15 days
Belarus	Three–four months
Armenia	Until smear microscopy conversion to negative is achieved; two consecutive negative smears a minimum of two weeks apart. According to the protocol (D10), XDR-TB cases must stay in a NTC TB hospital until the end of the intensive phase.
Viet Nam	As per PMDT guidelines in Viet Nam, MDR-TB treatment begins with an inpatient treatment phase of about 15 days; patients are discharged when they are stable and meet other PMDT requirements.
China	The first two months of the intensive phase
Kyrgyzstan	Not known
Georgia	Hospitalization time is until smear conversion and/or clinical improvement.
South Africa	MDR-TB patients are hospitalized until they are confirmed to be non-infectious. For XDR-TB patients, the duration of stay in the hospital may vary from patient to patient, depending on the clinical response to treatment; on average, the duration is six months.
Afghanistan	Not known

There is a strong regional trend with regard to a more centralized system in the countries in the CIS<sup>49</sup>; these countries are more likely to require compulsory hospitalization (four out of seven for MDR-TB). In addition, these countries tend towards a centralized approach to physician-initiated treatment, with five out of seven of these countries requiring doctors to initiate DS-TB treatment. This centralization is likely due to the models of financing operating in the region<sup>50</sup>. However, Russia's and Uzbekistan's policy change with regard to hospitalization indicates that the policy can be changed in a centralized setting with a similar model of health care financing.

## TB/HIV coinfection

Coinfection of TB/HIV is a considerable burden in several of the countries surveyed, even countries with low HIV burdens need to ensure that adequate provisions are made for TB/HIV coinfecting patients and that all TB patients are being screened for HIV and vice versa.

Tuberculosis is the most common presenting opportunistic disease and cause of mortality among people living with HIV, accounting for approximately 25% of all HIV-associated deaths annually. In the presence of HIV, TB is associated with substantially higher case fatality rates and is the most common notified cause of death. The high mortality rate in TB/HIV coinfecting patients is usually due to complications from overwhelming TB disease or impaired immunity from advancing AIDS. Evidence has shown that early ART initiation improves outcomes<sup>51,52</sup>. In light of this evidence, WHO policy states that ART should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count. TB treatment should



be initiated first, followed by ART as soon as possible within the first eight weeks of starting TB treatment. HIV-positive TB patients with profound immunosuppression (CD4 <50 cells/ $\mu$ l) should start ART within two weeks of starting TB treatment<sup>53</sup>.

Only four of the countries surveyed did not have guidelines recommending ART initiation regardless of CD4 count. The Russian Federation has a sliding scale of guidance regarding when to start ART in coinfecting patients, which depends on CD4 count. Pakistan has an absolute number (<400) for starting ART. For Viet Nam and Afghanistan no policy recommendations could be found for CD4 count.

With a high treatment burden on coinfecting patients, treatment should be as closely linked as possible to support adherence to both treatment regimens. This ideally should encompass treatment being offered in one facility by a single team of people. The process of referral between treatment facilities can cause considerable delays. For example, in one South African township, only 11% of HIV-infected patients with CD4 cell counts <50 cells/ $\mu$ l who were referred from TB services to separate HIV services started ART within four weeks of their TB diagnosis.<sup>54</sup>

Seventeen countries have policies regarding TB treatment initiation in facilities offering HIV care. With regard to starting HIV care in TB facilities, a number of countries have policies allowing treatment to be started after a patient's case has been reviewed or discussed with an HIV specialist. Despite concerns about the management of side effects due to the combination of TB medications and ARVs, it is possible to successfully fully integrate TB/HIV services in one clinic to reduce delays and the burden on patients, including opportunity costs.<sup>55</sup> Decentralizing TB/HIV care is also associated with better outcomes<sup>56,57,58</sup>. When TB services are decentralized, the plans should consider how this complements existing HIV services, especially in communities with high rates of coinfection. It is important that HIV programme staff be aware and involved in patient care to ensure that appropriate follow up is arranged once the patient has completed TB treatment.

**Countries that recommend initiation of TB treatment in facilities providing HIV care (17/24)**

India, Belarus, Mozambique, Pakistan, Viet Nam, China, Nigeria, DRC, Ukraine, Indonesia, Tajikistan, Georgia, Kenya, Zimbabwe, Brazil, South Africa, Swaziland

**Countries that recommend initiation of HIV treatment in facilities providing TB care**

Russian Federation, Belarus, Armenia, Viet Nam, China, Nigeria, Afghanistan, DRC, Kyrgyzstan, Uzbekistan, Ukraine, Indonesia, Tajikistan, Georgia, Kenya, Zimbabwe, PNG, Swaziland

## V. DRUG REGULATORY ENVIRONMENT

### Key findings

- Countries should have accelerated mechanisms in place for registration and importation of key DR-TB medicines to improve access to more effective treatment regimens.
- Countries should align their quality assurance mechanisms and standards for procurement of TB medicines with WHO recommendations.

### Accelerated approval for the registration of DR-TB medicines

Fifteen countries (please refer to summary table on policies in the section 'Conclusions and recommendations') have an accelerated approval mechanism in place that allows swift registration of DR-TB medicines including new drugs, even in cases when drugs have been previously registered by a stringent regulatory authority or prequalified by the WHO Prequalification Programme (PQP)<sup>59</sup>. Countries should participate in the collaborative registration procedure set by the WHO PQP, which allows for registration of a drug within three months for prequalified medicines. Even though this procedure requires pharmaceutical companies to request the registration in the first place at local regulatory agencies, it is free of charge and does not entail any dossier submission; countries can request that companies initiate the process for key medicines. Whenever countries are part of this procedure or have a national accelerated approval mechanism in place, they should uphold their commitment to fast-track evaluations.

Before registration takes place, it is important that countries be able to grant importation waivers to DR-TB medicines unregistered locally whenever they have already been prequalified by the WHO or have been granted full or conditional approvals by stringent regulatory authorities.

### Local registration of DR-TB medicines and their addition to the national essential medicines list (EML)

No country has registered the full set of DR-TB medicines recommended by the WHO guidelines and that may be required to treat the different resistance patterns that could be faced in DR-TB clinics. Granting importation waivers for unregistered DR-TB medicines is a helpful interim access strategy, but only local registration can ensure long-term supply.

The WHO updated its EML<sup>6</sup> in April 2015 with new DR-TB medicines (e.g. bedaquiline, delamanid) and also with key repurposed medicines that do not have official TB indications but have sufficient supportive data in the literature on their benefits for DR-TB (e.g. linezolid). Countries should update their national EML with all current TB medicines listed in the WHO EML to ease importation.

### Quality assurance

The source of funding for TB drugs and the procedure for countries to purchase them has a direct impact on the quality of the medicines, especially considering the varying stringency of national medicines regulatory authorities (NMRA) across countries. Furthermore, there is no harmonization even within countries in terms of the different purchase and mixed funding mechanisms for TB medicines.

Quality criteria differ depending on whether the purchases are covered by domestic funding or external donors like the Global Fund to Fight AIDS, TB and Malaria (GFATM), which link their grants to quality criteria of medicines set by the Global TB Drug Facility, for instance.

The possible withdrawal of GFATM financial support from TB programmes in a series of countries may lead National TB programmes to order DR-TB medicines with government money without a clear reference to WHO quality standards. Some countries also follow their own quality standards, but to ensure quality of drugs these standards need to be aligned with the global recommendations by WHO.





# **TB POLICIES: CASE STUDIES FROM THE FIELD**



## **BOOSTING SCALE-UP OF NEW DIAGNOSTICS: A TB REACH INITIATIVE FROM UGANDA**

In 2010, World Health Organization (WHO) recommended a rapid molecular test, Xpert® MTB/RIF, for the detection of HIV-associated pulmonary tuberculosis (PTB) as a replacement for smear microscopy. However, two years after the WHO recommendation, the National Tuberculosis Leprosy Programme (NTLP) of Uganda had still not yet adopted the new diagnostic protocol.

Uganda's national guidelines continued to recommend a chest radiograph after two negative sputum smears in patients presumed to have PTB. This approach posed a challenge for TB screening in HIV-infected patients because smear microscopy has low sensitivity among people with HIV. Furthermore, access to chest radiography can be severely restricted. Given these resource limitations, this NTLP diagnostic algorithm for smear-negative PTB often caused long delays prior to treatment initiation and involved patients making multiple visits to different health facilities. Such delays in diagnosis and treatment can prove life threatening and increase mortality in countries such as Uganda, which have a high incidence of both HIV and TB.

To help address this situation, the Foundation for Innovative New Diagnostics (FIND) and the NTLP applied and received funding from Stop TB Partnership through the TB REACH initiative. The initiative, which was launched on 15 November 2011, aimed to introduce Xpert as the initial means of diagnosing TB in HIV-infected patients at six district-level health facilities in Uganda. In addition, in order to overcome the difficulties of people with TB being lost to follow-up prior to diagnosis, a web-based electronic reporting system using mobile SMS for data entry and results feedback was developed and introduced in collaboration with Interactive Research and Development (IRD). This system is also being implemented as a key element of another TB REACH project in Pakistan.

Initially, Xpert was successfully implemented as an add-on diagnostic test for smear-negative HIV-positive patients presumed to have TB, at six sites serving an estimated total population of 8.6 million people. A total of 16224 presumptive TB individuals attending health facility outpatient departments underwent

TB sputum microscopy. Of these, 7551 HIV-positive patients who were presumed to have TB were tested using the Xpert test. Xpert found a total of 1043 individuals to be positive for TB. In the absence of this new technology, these individuals would not have been diagnosed as bacteriologically confirmed cases. After a year of implementation, the initiative began to use Xpert to directly test all people with HIV in need of further evaluation for TB. As of June 2015, a total of 10 013 HIV-positive patients were tested using Xpert, of which 1494 were found to be positive for TB.

The NTLP Strategic Plan (NTLP-SP) 2010/11–2014/15 has now been revised, including important changes related to collaboration between HIV and TB treatment programmes, and in particular, the need to scale up new diagnostics in Uganda.

## COMPASSIONATE USE OF BEDAQUILINE TO TREAT EXTENSIVELY DRUG RESISTANT TB (XDR-TB) PATIENTS IN ARMENIA

Multidrug-resistant tuberculosis (MDR-TB) poses a growing public health threat in Armenia, which currently ranks among the world's 27 countries with the highest MDR-TB burden<sup>60</sup>. In this context, extensively drug-resistant tuberculosis (XDR-TB) has also emerged, accounting for approximately 10% of diagnosed MDR-TB patients in 2011. Having worked in MDR-TB care in Armenia since 2005, Médecins Sans Frontières (MSF) worked with Ministry of Health officials to formalize a framework to allow compassionate use of new TB drugs for patients without any other treatment options. A committee of experts was convened to develop a protocol for the compassionate use of the new TB medicines, which was then approved by a local ethics committee and the Ministry of Health. A humanitarian waiver was granted to allow importation of the necessary drugs. An agreement to access bedaquiline was signed in 2012, and in July 2013, eligible patients began receiving treatment, with 62 patients having benefited to date. Patients receive a 24-week course of bedaquiline tablets, added to a multidrug TB regimen that lasts two years.

**Table 1:** Chronological milestones for the initiative

Late 1990s–early 2000s	TB control strategies based on DOTS started and expanded across Armenia
September 2005	MSF begins work on MDR-TB related projects in Armenia
December 2006	National tuberculosis control programme for 2007–2015 adopted by the government
Early 2012	MSF begins work to establish compassionate use of TB drugs in Armenia
October 2012	National TB Programme signs agreement Janssen to access bedaquiline through for compassionate use
2013	National response plan to combat drug-resistant TB 2013–2015 adopted by the government
January 2013	Armenian ethics committee and Ministry of Health approves use of bedaquiline on humanitarian grounds
February 2013	First bedaquiline request submitted to Janssen
March 2013	First bedaquiline importation through a humanitarian waiver system
April 2013	First patients begin receiving treatment with bedaquiline
April 2015	End of compassionate use of bedaquiline and beginning of routine use of bedaquiline supplied through the Global Drug Facility
Present	Continued implementation of compassionate use initiative led by MSF for other new drugs; Armenian government continues to implement routine use of bedaquiline through the National TB Programme

MSF supported Armenia's compassionate use initiative by providing guidance on technical aspects, as well as funding, procurement of drugs, training of providers and support for local TB specialists to deliver the new treatment. The compassionate use initiative is part of the National TB Programme's national policy framework for strengthening Armenia's response to MDR and XDR-TB.

## DECENTRALIZATION OF DIAGNOSIS AND TREATMENT OF DR-TB

### Khayelitsha, South Africa

In South Africa, tuberculosis (TB), including DR-TB, was the leading cause of death in 2012. In Khayelitsha, a township on the outskirts of Cape Town with a high prevalence of HIV, there are epidemic levels of DR-TB, including multidrug-resistant and extensively drug-resistant tuberculosis (MDR/XDR-TB). MSF, in collaboration with the local Department of Health, piloted a decentralized model of care whereby DR-TB patient care and support was made available at the primary health care level. The decentralized approach was started in 2007 and was handed over to the Department of Health in 2013, and the outcomes were analysed post-transition. In 2014, of the 190 DR-TB cases diagnosed in Khayelitsha, 183 (96.3%) received treatment through this decentralized model. Although the proportion of successful treatment outcomes (defined as treatment cure or completion) largely remained the same as those reported in other sub-districts and provinces, there was an increased proportion of prevalent DR-TB cases in the community accessing care due to decentralization of services. Crucially, costing studies have determined that a fully decentralized DR-TB model of care costs 42% less than a centralized hospital model.

In the Khayelitsha model, decentralization has improved access to TB care and treatment and has also resulted in reduced cost of treatment for the patient, including opportunity costs. As such, the model provides a valuable example that can be replicated in similar settings.

### The Karakalpakstan, Uzbekistan

Tuberculosis (TB), and particularly multidrug-resistant tuberculosis (MDR-TB), is a major public health concern in Uzbekistan. An estimated 23% of new TB cases are MDR-TB cases. In 2010, MDR-TB treatment required compulsory hospitalization in centralized hospitals for the initial few months of treatment.

As the numbers of diagnosed patients increased, a waiting list developed. In addition, many patients were not able to access the centralized services easily. In order to facilitate the decentralization of services, reduce waiting lists and facilitate the scale-up of drug-resistant TB treatment, the Ministry of Health in Uzbekistan, working with Médecins Sans Frontières, began to implement ambulatory care day 1 (ACD1). The goal was to initiate TB treatment in community settings closer to patients' homes.

In order to implement this change, a new legal framework was developed in conjunction with new treatment guidelines. Staff not previously involved in TB care management also had to be trained. Key challenges of integrating the diagnosis and treatment of drug-resistant and drug-sensitive TB care into primary health care centres included:

- Task shifting from central level specialists to family doctors, and the development and training of adherence support nurses;
- The formation of district level consiliums for decision-making and case review, and to support on-the-job training;
- Strengthened infection control and infrastructure investment;
- Introduction and scale up of rapid molecular diagnostic tests, with improved transportation of samples and communication of results.

Initially piloted in two districts in 2010, ACD1 has since been scaled up to all 16 districts in Karakalpakstan. Over half of patients commencing TB treatment now start on ambulatory treatment from day 1. The time from diagnosis to commencing treatment has been reduced, and there are no longer waiting lists for hospitalization..

## COUNTRY PERCEPTIONS ON THE IMPLEMENTATION OF THE NEW MULTIDRUG-RESISTANT TB (MDR-TB) MEDICINES

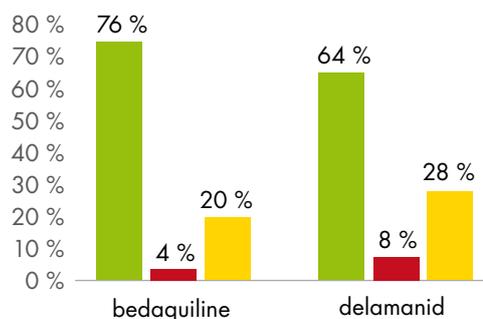
The current treatment for drug-resistant TB is long, complex, and associated with severe and life threatening side effects. Furthermore, the treatment only has successful outcomes for approximately 50% of people who start treatment. WHO has issued interim guidance on the use<sup>61</sup> of two new drugs registered for use in treating multidrug-resistant TB (MDR-TB), bedaquiline and delamanid. Although these medicines offer great potential for improving MDR-TB treatment, the scale-up of their use has been slow.

To learn countries' perspectives on the barriers to using these new drugs, as well as to understand countries' intentions to incorporate the new medicines into treatment regimens and policies, Stop TB Partnership collaborated with Médecins Sans Frontières (MSF) to conduct a survey on new TB drugs in March 2015 (separate from the survey on which the Out of Step report is based) among national TB programmes in high MDR-TB burden countries. The survey was sent to 27 countries, and 25 countries had responded by June 2015 when the survey was closed.

The results showed that 24 countries were aware of the new medicines, but only 28% had registered bedaquiline and 12% has registered delamanid for use. With regard to a framework for compassionate use or other mechanisms to enable pre-approval access, 68% of the countries accessed bedaquiline through such mechanisms, and 56% did so for delamanid. The most common reasons cited by countries for the limited or non-usage of the medicines were: (i) the lack of registration of the medicines in their country; (ii) economic barriers such as the cost of the medicine and/or companion medicines; (iii) concerns about the side effects; (iv) limited knowledge of the drugs; and (v) the lack of training for practitioners on how to administer the drugs.

When asked whether they would recommend the use of the new medicines, most countries responded that they were comfortable using the medicines and would strongly recommend their use for the treatment of MDR-TB.

**Table:** Would countries recommend the use of new medicines?



**Legend:** ● yes ● no ● I don't know

## A NEW APPROACH TO MDR TB TREATMENT

Access to diagnosis and treatment of MDR-TB (multi-drug resistant TB) is gradually being rolled out across high-burden countries. But the treatment is lengthy (20-24 months), includes 8 months of painful daily injections, and is toxic and expensive. In Uzbekistan, MSF is piloting a shorter treatment.

*I asked Nurlan\* to tell me the best thing about getting back to school. A shy 15-year old, living in Karakalpakstan, Uzbekistan, he said he was just happy to hang out with his friends again. Nurlan had become unwell in November 2013 and GeneXpert testing had confirmed he had MDR-TB. After counselling, Nurlan elected to trial the shortened regimen.*

The shortened regimen, developed in Bangladesh, is based on a recombination of first and second line TB agents taken over 9–11 months. It lacks some of the most side-effect prone agents of the standard treatment, such as cycloserine, known to cause psychosis. And it reduces the injection phase to 4–6 months, cuts the total number of tablets, and lowers the cost from around 3000 to 400 euros per patient. MSF has previously used the regimen in conflict settings where a 20-month regimen is unfeasible. But more robust evidence of its efficacy is needed. The ongoing, randomised controlled STREAM trial<sup>62</sup> is examining whether the shortened regimen is non-inferior to the current standard of care. But it isn't designed to answer the practical questions of how to implement the regimen safely, and it excludes children and regions with high levels of second line drug resistance. These issues led to MSF's decision to pilot the shortened treatment in a prospective cohort in Uzbekistan.

Recruitment in Uzbekistan was completed in March 2015, with the enrolment of 146 patients. Full results are due in January 2017, one year after the final patient completes treatment. So far, some patients have found the regimen easier to tolerate. Early results<sup>63</sup> indicate that sputum culture conversion may occur faster than with the standard regimen. Most importantly, patients can see an end to their treatment. The regimen is unlikely to be a panacea, however, particularly in areas with high levels of second-line drug exposure, since it is unlikely to be effective in patients who have previously taken these drugs. Additionally, patients still experience nausea, headache, and joint pains. Nevertheless, a shortened regimen would reduce the impact on patients' lives, lessen the financial burden for programmes, and provide a simpler comparison for newer drugs in trials, which currently must include comparison to the lengthy standard of care. Interim data from the MSF studies in Uzbekistan have been included in an individual patient data meta-analysis for the upcoming WHO TB guidelines revision which is due out in 2016.

Nurlan finished treatment in September 2014; the first child ever to have completed treatment with the shortened regimen. He was able to return to school just 5 months after starting treatment. He has now completed 12 months of post-treatment follow-up without evidence of relapse. We wait impatiently for the final study results, to learn whether this regimen could benefit the thousands of patients around the world like Nurlan. TB is now the biggest infectious diseases killer globally, and one of the major causes of morbidity and mortality in many of the countries where MSF works. There is an urgent need for improved regimens and programme delivery to help us respond appropriately to the needs of patients and communities.

\*Name changed to maintain anonymity.



## INTRODUCTION OF NEW PEDIATRIC FDCS: KENYA EXPERIENCE

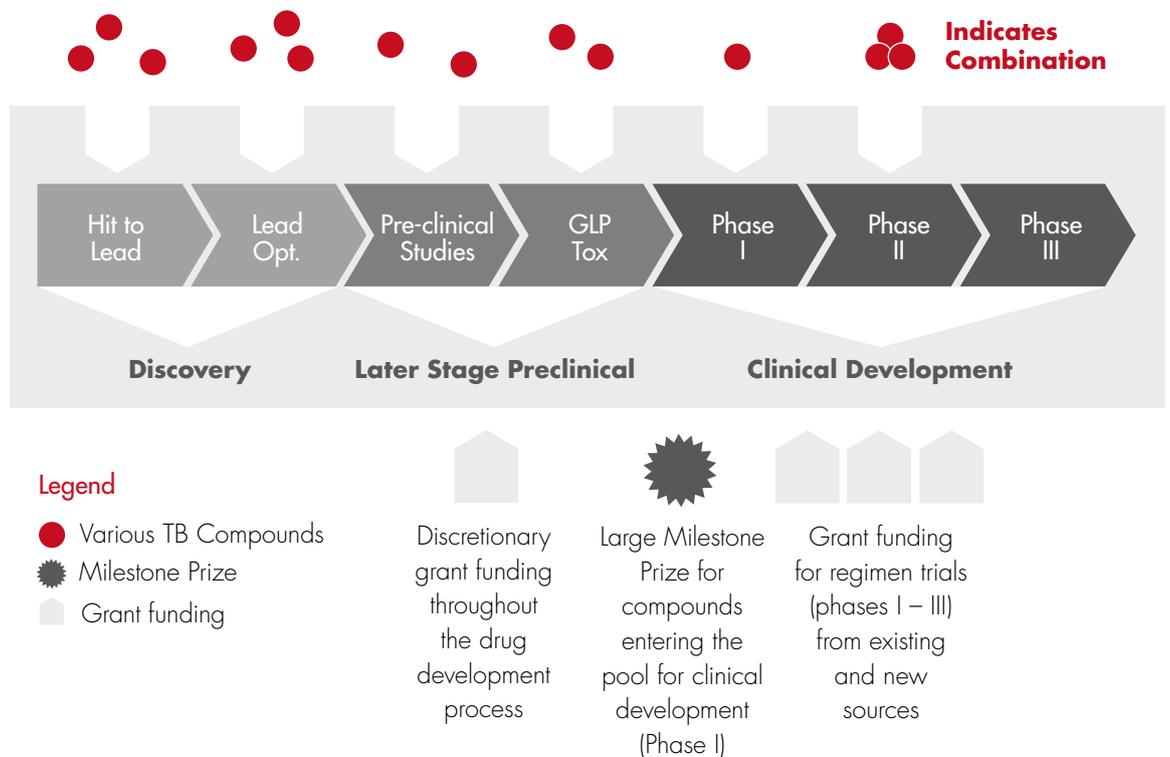
The treatment course for drug-susceptible TB (DS-TB) in children has the same drugs as used for adults, but recent changes in the doses of these medications has resulted in the current fixed dose combination (FDC) tablets being no longer appropriate. WHO issued interim guidance in 2010 on the increased doses and temporary dosing tables showing how to use the existing FDC products in combination with mono-substances. In 2013, the TB Alliance, in partnership with WHO Essential Medicines department, received a UNITAID grant to develop the appropriate FDC formulations, which are easier to prescribe and administer to children. As well as working with manufacturers to define the product, the TB Alliance worked on identifying and mapping paediatric TB purchaser landscapes, identifying barriers to product uptake in the 22 high-burden countries, and worked with countries to include childhood TB in national strategies/plans, budgets, and grant applications/renewals.

In Kenya, TB Alliance supported the government to request the manufacturer of one of the approved FDCs to commence the product registration process with the Kenyan drug regulatory authority. The registration process should be finalized by the end of 2015, when Kenya will place the first order for the new RHZ (75/50/150) and RH (75/50) dispersible products, becoming available for use in March/April 2015. While waiting for the new products, the Kenyan NTP developed a phase-out plan for the existing older dosage paediatric FDCs already in the country. The phase-out plan of the older formulations included training of facility staff on use of the new paediatric FDC products, issuance of a circular to facilities on use of the new products, and review of the current treatment guidelines to ensure they match current WHO guidelines.

## THE 3P PROJECT

The '3P Project' aims to rapidly deliver affordable, effective new regimens for TB using push, pull and pool mechanisms to foster an open collaborative approach to conducting drug development and to employ novel approaches to financing and coordinating R&D. The 3P Project implements three mechanisms to facilitate the necessary and appropriate R&D for TB regimens:

- pull funding to incentivise R&D activities through the promise of financial rewards on the achievement of certain R&D objectives (i.e. through milestone prizes).
- pooling of intellectual property (IP) and data to ensure open collaborative research and fair licensing for competitive production of the final products.
- push funding to finance R&D activities upfront (i.e. through grants).



For more information, please visit <http://www.msfacecess.org/3p>



# **CONCLUSIONS AND RECOMMENDATIONS**

With a confluence of changes affecting both the TB epidemic and the global response to it, now is the time to capitalize on international consensus around more ambitious post-2015 targets and innovative thinking about the future of the global TB response, including more effective and easier to use diagnostic and treatment approaches.

Each country in this survey has different strengths and areas for improvement, and countries, implementers and donors must consider how to build on the strengths and address policy gaps on a country-by-country basis. TB-endemic countries, WHO, manufacturers, donors and treatment providers must work together to close the deadly gaps in diagnosis and treatment of people with TB.

The first step in ensuring that all patients with TB get the best possible treatment and are able to benefit from recent advances in TB diagnostics and care is to ensure that national policies are up to date with international guidance. Once national policies are updated, then countries must tackle the more difficult task of ensuring that these policies are implemented countrywide. Only with the right policy environment, political will at the global and national levels, and adequate financing to support the implementation of policies can the current gaps that beset TB programmes be addressed. This will allow the necessary paradigm shift and bending of the curves to end TB once and for all.

## COUNTRIES

- Increase domestic financing and high-level political commitment to ensure that implementation of diagnostics is in line with national policies.

## DIAGNOSIS:

- Reduce the significant gaps between policy and implementation.
- Provide DST for all re-treatment cases, and avoid use of Category II treatment; when DST is not available, empirical MDR-TB treatment can be considered while awaiting DST in high MDR-TB burden areas.
- Strategically invest resources to achieve wider diagnostic coverage and improve access to laboratory confirmed diagnosis and DST.

## MODELS OF CARE:

- Provide ambulatory decentralized and integrated care for DRTB and DS-TB.
- Remove policies of compulsory hospitalization for TB patients, and have hospitalization depend on clinical need.
- Ensure TB/HIV services are jointly planned and patients are effectively managed in each service.

## DS-TB TREATMENT PROTOCOLS:

- Ensure daily treatment for TB is the standard of care.
- Adopt and promote the use of quality assured FDCs in adults and children, by including FDCs in national guidelines, as well as in national EMLs in order to reduce the use of mono-substance formulations for DS-TB treatment in adults and children.
- Phase out the use of Category II re-treatment regimen.

## DR-TB TREATMENT PROTOCOLS:

- Ensure that national TB treatment guidelines and EMLs are in line with WHO guidance for DR-TB and include necessary group 2,3,4 and 5 drugs.
- Implement the necessary legislation for CU as soon as possible. There should be parallel efforts to register new drugs so that they are available to more patients and a sustainable supply can be set up.

## DRUG REGULATORY ENVIRONMENT:

- Ensure procurement and use of quality-assured (including WHO prequalified and stringent regulatory authorities approved) TB drugs.
- Promote capacity of national medicine regulatory agencies (NMRA) to assess quality of TB medicines.
- Put in place procedures that allow importation and dispensation of quality-assured group 5 medicines not yet registered.
- Enable fast track registration procedures of priority TB medicines.
- Make use of international regulatory flexibilities, such as the collaborative registration process at the WHO prequalification programme, and recognize market authorizations granted by stringent NMRAs for priority medicines.

## MANUFACTURERS

### Prepare for scale-up of new treatments:

- Provide access to innovative TB medicines through CU.
- Proactively register new medicines in countries where clinical trials take place and other high-burden TB countries, and register medicines and new compounds, even in small markets.
- Ensure an affordable, transparent price for all DR-TB medicines for all low- and middle-income countries.
- Accelerate combined drug research to create appropriate regimens.
- Ensure that intellectual property barriers (patents and test data) do not preclude generic competition or development of appropriate FDCs or other formulations.
- Introduce new diagnostic technologies.
- Develop diagnostic assays for rapid detection of drug resistance in decentralized settings and ensure adequate distribution networks and adherence to negotiated prices for products; offer contracts that allow for reagent rental and flexible and transparent pricing structures for tests to allow for bundling or unbundling of maintenance contract costs, depending on country needs.

## DONORS

- Increase political and financial support for adoption and roll-out of optimal TB/DR-TB policies and practices, including decentralized and integrated (TB/HIV) services.

- Support the development of new innovations and assist with drug regulatory policies for quality-assured TB medicines.
- Assist with determining optimal implementation models, strengthening laboratory networks, referral systems and roll-out of diagnostics, and research and development including through innovative models such as the 3P project.

## WORLD HEALTH ORGANIZATION

- Continue to issue policy guidelines for TB at international level and facilitate policy change at country level to support rapid adoption of international guidance into national TB policies.
- Ensure a timely and transparent process for identifying and approving new diagnostic technologies.
- Ensure policies are relevant and translatable to countries with an appropriate level of technical assistance by technical partners to support the implementation of policies.



# KEY TB POLICIES DASHBOARD





**KEY INDICATORS**

Decentralization of DS-TB treatment initiation at primary health care level

Nurses or health workers can initiate DS-TB treatment

TB treatment initiation in facilities providing HIV care

Routine hospitalization of MDR-TB patients not recommended

There is a process for accelerated registration of DR-TB drugs, including new TB drugs

**MODELS OF CARE**

**DRUG REGULATORY ENVIRONMENT**

**LEGEND**



**Disclaimer:** The above reflects only policy status and is not related to access or actual implementation status



# **GLOSSARY**

**Active case finding:** Strategy of actively screening and diagnosing individuals belonging to groups at high risk for TB (e.g. people living with HIV, miners, etc.). Risk groups vary depending on the epidemiological profile of TB in a given country.

**Category II (Category 2) treatment:** One drug, streptomycin, is added to standard first-line drugs and the regimen is extended to eight months. WHO has recommended that this treatment option only be considered in areas at low risk for MDR-TB.

**Clinical trials:** Sets of tests in medical research and drug development that generate safety and efficacy data (including information about adverse drug reactions and the adverse effects of other treatments) for health interventions (e.g. drugs, diagnostics, devices, therapy protocols).

**Compassionate use:** The terms “compassionate use,” “expanded access” or “special access” have essentially the same meaning. They refer to programmes that are intended to provide potentially lifesaving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists and/or patients who cannot enter a clinical trial. Compassionate use refers to programmes that make medicinal products available either on a named-patient basis or to cohorts of patients. Compassionate use needs to be framed within a national legislation that establishes the conditions under which the drug is made available. Refer to Annex 5 (Use of experimental drugs outside of clinical trials “compassionate use”) of the “WHO guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008”.

**Contact tracing:** The identification, screening and testing of individuals who have been in close contact with an individual who has infectious TB, and therefore at high risk of having contracted TB. Please consult [http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf).

**Culture:** Bacterial culture is a laboratory method to multiply bacteria in order to assess whether they are present or not in a patient’s sample. This is done by letting the bacteria grow in a predetermined culture medium under controlled laboratory conditions outside of the natural environment where they usually grow (e.g. for TB, the human body).

**Culture-converted:** A person whose last two clinical samples are no longer growing *M. tuberculosis*, implying that the bacteria are no longer present.

**Drug resistance:** When a drug used to treat tuberculosis is in fact ineffective against a strain of *M. tuberculosis*, the bacteria are said to be resistant to the drug (as opposed to drug-susceptible or drug-sensitive).

**Drug-susceptible/drug-sensitive TB:** Bacteria are said to be sensitive to a drug when the drugs are effective in killing or stopping the multiplication of bacteria in the body and can therefore clear the infection. The strains of TB that are sensitive to all first-line drugs are called drug-susceptible.

**Drug resistant TB:** Broad term to take in all forms of drug resistant TB, including MDR-TB and XDR-TB. Extensively drug-resistant TB: see XDR-TB

**External quality assessment (EQA):** A system for objectively checking the laboratory’s performance using an external agency or facility. EQA allows for the comparison of a laboratory’s testing to a source outside of the laboratory, such as the performance of a peer group of laboratories or the performance of a reference laboratory. Please consult [http://www.who.int/ihr/training/laboratory\\_quality/10\\_b\\_eqa\\_contents.pdf](http://www.who.int/ihr/training/laboratory_quality/10_b_eqa_contents.pdf)

**Extrapulmonary TB:** A form of TB in which *M. tuberculosis* infects parts of the body other than the lungs, most commonly the lymph nodes, bones, central nervous system, and cardiovascular and gastrointestinal systems.

**First-line drugs:** The drugs used as the first resort to treat a disease. In the case of TB, the following four drugs are usually chosen: isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z). These drugs are highly effective in treating drug-susceptible TB, and patients usually tolerate them well. Streptomycin (S) is an injectable that is used in the first-line treatment of TB meningitis.

**Global Fund:** The Global Fund to Fight AIDS, Tuberculosis and Malaria is an international financing institution that invests the world's money to save lives. It invests in 150 countries to support the large-scale prevention of the three diseases through treatment and care programmes. It channels 82% of the international financing for TB.

**Group 5 TB medicines:** Anti-tuberculosis drugs with unclear efficacy or an unclear role in MDR-TB treatment as per WHO MDR-TB guidelines (i.e. they are not recommended by WHO for routine use in MDR-TB patients). Key medicines are clofazimine, linezolid and imipenem/cilastatin.

**Low-income country (LIC):** The World Bank's income classification for economies with a gross national income per capita of US\$ 1045 or less for the World Bank fiscal year 2015. Please consult <http://data.worldbank.org/about/country-and-lending-groups>.

**Lower-middle-income country (LMIC):** The World Bank's income classification for economies with a gross national income per capita of more than US\$ 1045 but less than US\$ 4125 for the World Bank fiscal year 2015. Please consult <http://data.worldbank.org/about/country-and-lending-groups>.

**Microscopy:** Currently the most commonly used technique to diagnose TB. Two to three sputum samples are taken from the patient. The sample is stained and later read under the microscope. If TB bacilli are present, they are visible in the form of small red rods, while the rest of the sample is blue.

**Multidrug-resistant TB (MDR-TB):** Patients are said to have multidrug-resistant TB, or MDR-TB, when they are infected with strains of TB that are resistant to (at least) the two most powerful first-line antibiotics used to treat TB, namely rifampicin and isoniazid.

**Mycobacteria:** Types of bacteria of the genus *Mycobacterium* that cause diseases such as TB and leprosy.

**M. tuberculosis:** *Mycobacterium tuberculosis* is a pathogenic bacterial species of the genus *Mycobacterium* and the causative agent of most cases of TB, first discovered in 1882 by Robert Koch.

**Point-of-Care testing (POC):** Diagnosis is carried out as close as possible to the site of patient care. The driving notion behind point-of-care testing is to have a test be as convenient for the patient as possible and to give immediate results leading to the prompt initiation of treatment.

**Pulmonary TB:** Form of TB where *M. tuberculosis* bacteria infect the lungs.

**Second-line drugs:** Second-line drugs are used when first-line drugs are no longer effective in curing a patient. In the case of TB, these drugs are less effective and have many more side-effects than first-line drugs. This report looks at the sources and prices of second-line anti-TB medicines classified as WHO Groups 2 (injectable agents), 3 (fluoroquinolones), 4 (oral bacteriostatic second-line agents) and 5 (agents with unclear efficacy), as well as new drugs like bedaquiline.

**Stringent regulatory authority (SRA):** An SRA is defined as an International Committee on Harmonization (ICH) member country, an ICH observer or any country whose regulatory authority is associated with an ICH member through a legally binding mutual recognition agreement, or be approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Art. 58 of European Union Regulation (EC) No. 726/2004 or United States FDA tentative approval. Please consult <http://www.ich.org>.

**Upper-middle-income country (UMIC):** The World Bank's income classification for economies with a gross national income per capita between US\$ 4125 and US\$ 12 748 for the World Bank fiscal year 2015. Please consult <http://data.worldbank.org/about/country-and-lending-groups>.

**WHO Prequalification (PQ) Programme:** The Prequalification Programme, set up in 2001, is a service provided by WHO to facilitate access to medicines that meet the unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. Please consult <http://apps.who.int/prequal/>.

**XDR-TB (Extensively drug-resistant TB):** Patients are described as suffering from extensively drug-resistant TB or XDR-TB when they have MDR-TB and also show resistance to second-line drugs, including at least one from the class known as fluoroquinolones and one of the injectable drugs.

## ABBREVIATIONS

<b>BRICS</b>	Brazil, Russia, India, China and South Africa
<b>CIS</b>	Commonwealth of Independent States
<b>DR-TB</b>	Drug-resistant tuberculosis
<b>DS-TB</b>	Drug-sensitive tuberculosis
<b>EQA</b>	External quality assessment
<b>FDC</b>	Fixed-dose combination
<b>FSU</b>	Former Soviet Union
<b>GFATM</b>	Global Fund to Fight AIDS, Tuberculosis and Malaria
<b>HIV</b>	Human immunodeficiency virus
<b>LIC</b>	Low-income country
<b>LMIC</b>	Lower-middle-income country
<b>MDR-TB</b>	Multidrug-resistant tuberculosis
<b>MIC</b>	Middle-income country
<b>MSF</b>	Médecins Sans Frontières
<b>NGO</b>	Nongovernmental organization
<b>NMRA</b>	National medicines regulatory authority
<b>NTP</b>	National Tuberculosis Programme
<b>STG</b>	Standard treatment guidelines
<b>TB</b>	Tuberculosis
<b>UMIC</b>	Upper-middle-income country
<b>USAID</b>	US Agency for International Development
<b>WHA</b>	World Health Assembly
<b>WHO</b>	World Health Organization
<b>XDR-TB</b>	Extensively drug-resistant tuberculosis



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**Disclaimer:** This report does not contain individual opinions of the organizations and is based on information from key informants. Stop TB Partnership and MSF have made every effort to ensure the accuracy of the data in this report, but we make no representations or warranties, either expressed or implied, as to their accuracy, completeness or fitness for a particular purpose.



# ANNEXES

# I. DIAGNOSIS POLICY TABLE

	AFGHANISTAN	ARMENIA	BELARUS	BRAZIL
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended as the initial diagnostic tests for all people (adult and children) in whom TB is presumed, i.e. symptomatics being investigated for TB, rather than sputum smear microscopy (SSM) and/or culture and DST				 (subnational)
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended as the initial diagnostic test for adults and children at risk of drug-resistant TB (DR-TB) and HIV-associated TB (high-risk groups)				
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended for already diagnosed TB patients with the purpose of testing or screening for identification of drug resistance.				
The rapid molecular diagnostics recommended by the NTP for the testing algorithms described in question 1, 2 and 3 are: WHO approved/ Not approved by WHO	WHO approved	WHO approved	WHO approved	WHO approved
IF YES to question 2 or question 3: specify groups of people or TB patients groups for whom guidelines recommend Xpert MTB/RIF	Routine culture, Xpert MTB/RIF and DST is recommended for below risk groups: Failure of treatment of Cat-I and Cat-II, Failure of anti-TB treatment in the private sector, MDR-TB contact, Exposure to institution that have MDR-TB outbreaks or high MDR-TB prevalence, Residence in area with high MDR-TB prevalence, Relapse and return after default, History of using anti-TB drugs of poor or unknown quality, Comorbid condition associated with malabsorption or rapid transit diarrhea, TB/HIV comorbidities	All smear-negative TB suspects	Diagnosed TB patients for DR, Initial diagnostic test for adults and children at risk of drug-resistant TB (DR-TB) and HIV-associated TB (high-risk groups)	Re-treatment cases, PLHA, Prisoners, Homeless, Health professionals, Indigenous populations, Failure of 1st line scheme, Sm +ve on 2nd month of treatment
First-line Drug DST (including at least rifampicin and isoniazid) is recommended for all rifampicin resistant (RR)-TB cases and for patients considered at risk of DR-TB				
Specify patient's groups for whom first-line drug DST is recommended	All RR cases to formulate SLDs treatment	All TB suspects and TB confirmed cases either by smear microscopy / Molecular tests are exposed to first-line DST (after culture is found +); Implemented YES	Done routinely for all patients	All TB cases diagnosed through Xpert should be conducted to culture and DST and mainly all symptomatic suspects with smear microscopy diagnosis. Re-treatment cases and vulnerable populations also should be sent to culture and DST.
Second-line DST (including at least fluoroquinolones and second-line injectable agents) is recommended for all Rif-resistant TB (RR-TB), polydrug-resistant (PDR)-TB and MDR-TB cases				

LEGEND  Yes  No

CAMBODIA	CHINA	DRC	GEORGIA	INDIA
				
				
				
WHO approved	WHO approved and ; Not Approved for Smear negative(TB suspects) by CFDA	WHO approved	WHO approved	WHO approved
MDR-TB suspects: (i)sputum non-converters and (ii) all re-treatment cases, in addition to (iii)symptomatic contacts of known DR-TB cases; (iv) people living with HIV	For smear-positive cases ; Implemented YES	Re-treatment cases, positive controls after months 3 and 5 of first treatment, MDR-TB contact cases, HIV-positive case Suspected of TB, cases with clinical and chest X-ray suggestive of TB but with AFB smear negative.	All TB suspects including adults and children	Paediatric cases, EPTB samples, HIV+, Presumptive DRTB
				
<ul style="list-style-type: none"> <li>• Re-treatment cases</li> <li>• Sputum non-converters (among new smear positive patients) at months 2 or 3</li> <li>• Symptomatic contacts of DR-TB cases</li> <li>• TB/HIV patients</li> </ul>	High-risk group (Failure with CAT I treatment, no smear conversion after two months treatment, The chronic, MDR-TB contacts, Relapse)	All RR cases and all primary culture positive cases	All groups – whenever culture is positive.	Rif resistance is considered as surrogate for MDR-TB eligible for second-line treatment
				

# I. DIAGNOSIS POLICY TABLE (CONT'D)

	INDONESIA	KENYA	KYRGYZSTAN	MOZAMBIQUE
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended as the initial diagnostic tests for all people (adult and children) in whom TB is presumed, i.e. symptomatics being investigated for TB, rather than sputum smear microscopy (SSM) and/or culture and DST	●	●	●	●
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended as the initial diagnostic test for adults and children at risk of drug-resistant TB (DR-TB) and HIV-associated TB (high-risk groups)	●	●	●	●
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended for already diagnosed TB patients with the purpose of testing or screening for identification of drug resistance.	●	●	●	●
The rapid molecular diagnostics recommended by the NTP for the testing algorithms described in question 1, 2 and 3 are: WHO approved/ Not approved by WHO	WHO approved	WHO approved	WHO approved	WHO approved
IF YES to question 2 or question 3: specify groups of people or TB patients groups for whom guidelines recommend Xpert MTB/RIF	DR-TB presumptive cases, including contacts, PLHIV presumptive for TB, New smear-positive cases (limited scale), Smear-negative cases (limited scale), Prisoners (limited scale), Children (pilot for close contact cases)	MDR TB Surveillance: All retreatment cases: a) Failures b) Relapses c) Return after default; DR-TB contacts; Smear-positive refugees; Health care workers with TB TB Diagnosis; HIV positive Smear negative; Diagnosis of TB in children; TB screening for the symptomatic patients for and on IPT	Re-treatment cases, children, MDR-TB contacts, severe clinical condition, HIV positives, unknown HIV status in high-risk setting, migrants, prisoners, ex-prisoners	Re-treatment TB cases, Pt with BK+ at 2 months old HIV patients and other immunological depressed pts, diabetics, Health staff, miners and prisoners, Endemic DR TB prevalence areas pregnant women and children
First-line Drug DST (including at least rifampicin and isoniazid) is recommended for all rifampicin resistant (RR)-TB cases and for patients considered at risk of DR-TB	●	●	●	●
Specify patient's groups for whom first-line drug DST is recommended	Yes for all RR confirmed TB cases from all mentioned at point 5	TB patients on re-treatment, health care workers, symptomatic contacts of drug resistant TB, smear-negative PLHIV, Patients returning after default (RAD), Lack of smear conversion at mo 2 while on 1st line treatment	All drug-sensitive bacteriological cases require first-line DST	Previously treated for TB; New cases that do not convert after month 2; MDR-TB contacts; HIV Patients; Health Workers; Prisoners; Miners; Pregnant women and Children; People from endemic areas, etc
Second-line DST (including at least fluoroquinolones and second-line injectable agents) is recommended for all Rif-resistant TB (RR-TB), polydrug-resistant (PDR)-TB and MDR-TB cases	● simultaneously for all mentioned at point 9	●	●	●

LEGEND  Yes  No

NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION	SOUTH AFRICA
				
				
				
WHO approved	WHO approved	WHO approved	WHO approved	WHO approved
Evaluation for DRTB a. Symptomatic contacts of DRTB cases b. Failure of regimen 1 c. Failure to convert (smear positive to smear negative ) after repeat AFB microscopy follow-up examination at the end of the third months of regimen 1 treatment d. All patients who have been previously treated for TB	All presumptive /diagnosed TB cases with history of previous treat. Presumptive TB case under 15, and HIV +, immune-compromised, hospitalized, HCW and EPTB presumptive – and presumptive TB case in whom specimen is obtained through some procedures eg. Bronchial Lavage	Previously treated; Non converter (at the end of 2 months); HIV positive; Symptomatic contact of known MDR-TB; Staff of health facilities	For all (adult and children) in whom TB is presumed	TB and DRTB contacts, Non-contact symptomatic individuals, Re-treatment after relapse, failure and default
				
RR-TB patients following Xpert	All detected RR on Xpert- Others at high suspicion of drug resistant by Rif susceptible on Xpert	All R-resistant cases	All TB patients	All new patients
	 for all RR ;			

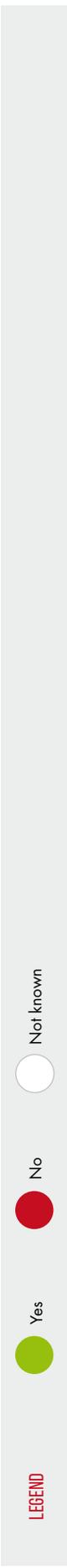
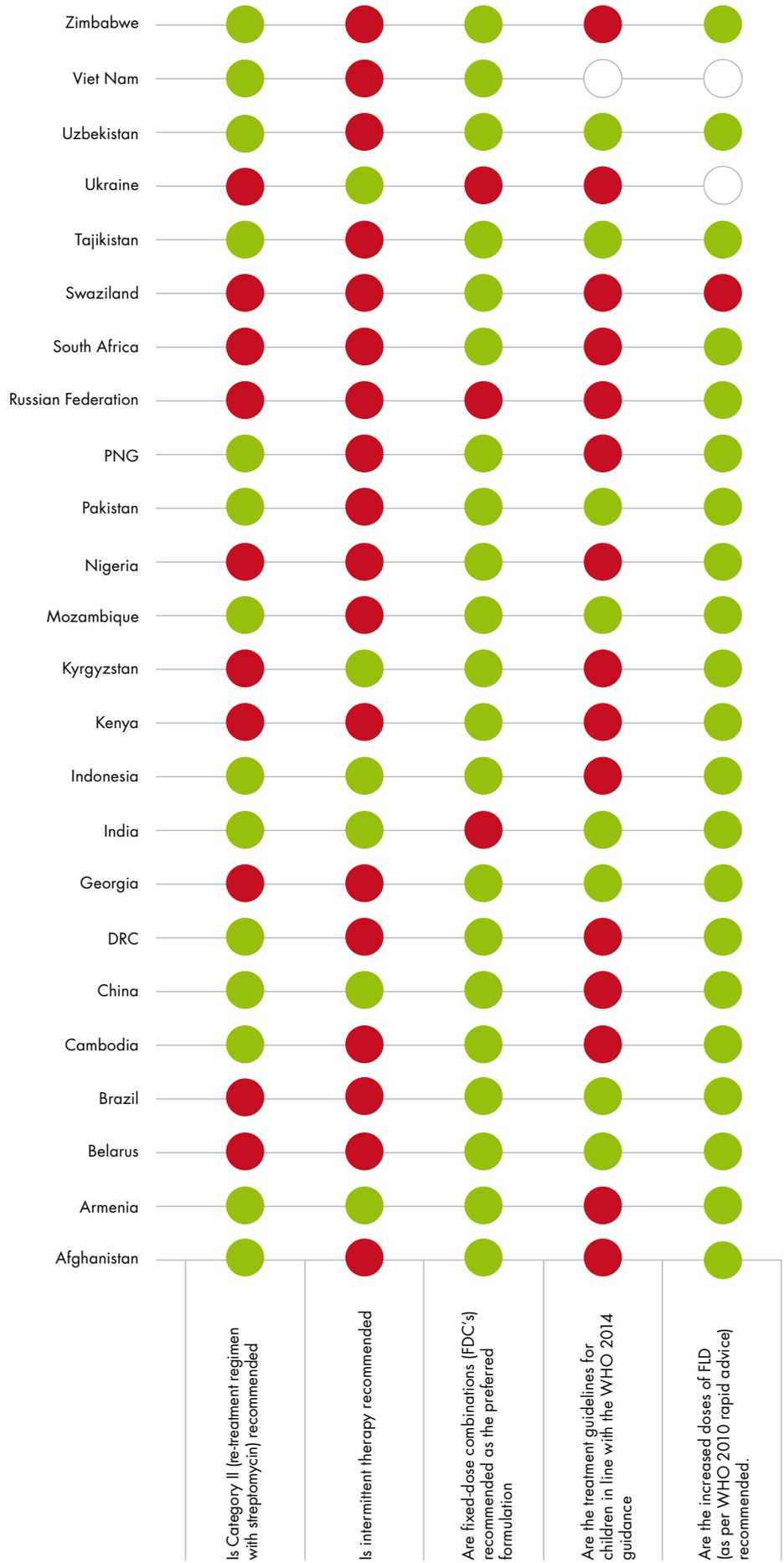
# I. DIAGNOSIS POLICY TABLE (CONT'D)

	SWAZILAND	TAJIKISTAN	UKRAINE
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended as the initial diagnostic tests for all people (adult and children) in whom TB is presumed, i.e. symptomatics being investigated for TB, rather than sputum smear microscopy (SSM) and/or culture and DST			 (subnational)
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended as the initial diagnostic test for adults and children at risk of drug-resistant TB (DR-TB) and HIV-associated TB (high-risk groups)			
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended for already diagnosed TB patients with the purpose of testing or screening for identification of drug resistance.			
The rapid molecular diagnostics recommended by the NTP for the testing algorithms described in question 1, 2 and 3 are: WHO approved/ Not approved by WHO	WHO approved	WHO approved	WHO approved
IF YES to question 2 or question 3: specify groups of people or TB patients groups for whom guidelines recommend Xpert MTB/RIF	Xpert is recommended to all TB suspects, including congregate settings, (ex)miners, children,	TB cases enrolled in treatment as Category I, II and III, smear-positive and/or with progressive clinical and X-ray course after intensive phase; Re-treatment cases without RR testing; MDR-TB contacts; or individuals from DR-TB risk groups (e.g., treatment defaulters, deceased due to TB, etc.); Penitentiary detainees suspected of TB; patients with progressive TB; TB suspected cases with the history of non-standard treatment; HIV-positive individuals; TB diagnosis, without data on drug resistance; Suspected of TB; Healthcare and penitentiary facilities' staff suspected of having TB; Migrant workers suspected of having TB; Pregnant women and women after childbirth suspected of having TB; Sputum SM(-)ve cases without positive clinical and X-ray course after treatment with broad spectrum antibiotics.	As initial test for all TB patients who start TB treatment like initial test, TB patients who have SS+ after 90 dose
First-line Drug DST (including at least rifampicin and isoniazid) is recommended for all rifampicin resistant (RR)-TB cases and for patients considered at risk of DR-TB		 First-line drug DST is recommended for all rifampicin resistant (RR)-TB cases and patients considered at risk of DR-TB	
Specify patient's groups for whom first-line drug DST is recommended	All patients with Xpert positive	All suspected to TB cases; relapse; treatment failed. From KNCV According to the National Guidelines on DR-TB first-line drug DST is recommended to conduct for all detected TB patients	New cases (Cat I, III) and Cat II (Previously treated cases and relapses).
Second-line DST (including at least fluoroquinolones and second-line injectable agents) is recommended for all Rif-resistant TB (RR-TB), polydrug-resistant (PDR)-TB and MDR-TB cases		 Second-line DST (including at least fluoroquinolones and second-line injectable agents) is recommended for all Rif resistant TB (RR-TB), polydrug-resistant (PDR)-TB and MDR-TB cases From KNCV Because of the high proportion of resistant strains among new and recurrent cases in Tajikistan, it recommended a survey of all MDR-TB cases. DST for first-line anti-TB drugs should be part of the diagnostic minimum. Moreover, at least it recommended a survey of all MDR-TB strains for resistance to second-line anti-TB drugs, using the recommended hierarchy of DST	

LEGEND  Yes  No

UZBEKISTAN	VIET NAM	ZIMBABWE
 (subnational)		
		
		
WHO approved	WHO approved	WHO approved
HIV coinfectd (check)	See comments box	All HIV-positive patients suspected of TB, all HIV-negative patients suspected of TB with risk factors for MDR-TB, all HIV-negative patients suspected of TB that are sputum negative on microscopy, Children with presumptive TB, All re-treatment patients, Health care workers suspected of TB, Presumptive TB cases with a history of travel to countries with high DR-TB burden, Contacts of DR-TB patients
		
KK: All TB patients diagnosed with rapid molecular method, who have positive culture AT national level: All patients with positive smear, MBTT+ / Rif – R and Rif – S by GX, and those with positive results by Hain ver. 2	See above, however in practice DST is infrequent due to inconvenience of travelling to DST, time requirements and user fees	Patients with no resistance to first-line TB drugs. People at risk for DR-TB, Xpert positive but no Rifampicin resistance, do culture and 1st line DST DR-TB guidelines, page 15
	 Implemented Yes but may not be widely	 (subnational)

# II. DS-TB TREATMENT REGIMENS





# III. DR-TB TREATMENT REGIMENS

	AFGHANISTAN	ARMENIA	BELARUS	BRAZIL
National treatment guidelines reflect WHO drug-resistant treatment guidelines including group 5 drugs.	 group 5 drugs are not recommended		 ;	
If NO what drugs are not included and/or what is missing from the national guidance.	8(Am-Lfx-Eto-Cys-ZVB6)/ 16 (Lfx-Eto-Cys-ZVB6). - For cases with frequent use of fluoroquinolone, PAS is added. - For some cases reaction or resistance to Aminoglycosides Cm replace for Am			kanamycin, cycloserine, prothionamide, thioacetazone e clarithromycin
There are guidelines on the use of the bedaquiline				
There are guidelines on the use of delamanid		In process		
Before registration, new and repurposed drugs are available through compassionate use or expanded access programmes or any other legal mechanisms. If yes, which one of these mechanisms is in place:		 CU mechanism		
All group 2 drugs are on the national essential medicines list (EML)				
If NO, which drugs are not included.				kanamycin
All group 3 drugs are on the national EML		 levofloxacin, moxifloxacin, ciprofloxacin		
If NO, which drugs are not included				
All group 4 drugs are on the national EML		 cycloserine, ethionamide, prothionamide		
If NO, which drugs are not included.	All members except Eto, PAS and Cys			cycloserine, prothionamide
All group 5 drugs are on the national EML		 imipenem, cilastatin, clarithromycin are in the EML clofazimine, linezolid, amoxicillin / clavulanate, thioacetazone are not mentioned in the EML		
If NO, which drugs are not included.	All except co-amoxiclave and clarithromycin	clofazimine; linezolid, bdq,		amoxicillin/clavulanate, thioacetazone, imipenem/ cilastatin

LEGEND  Yes  No  Not applicable

CAMBODIA	CHINA	DRC	GEORGIA
			
			
			
			
			
			No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.
			No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.
			No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.
			No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.
			No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.
		terizidone	No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.
			No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.
	clofazimine, linezolid, thioacetazone, imipenem/cilastatin	linezolid	No valid Georgian National EML exists; it is in the process of being finalized and approved. Meanwhile, WHO EML is used as a reference.

### III. DR-TB TREATMENT REGIMENS (CONT'D)

	INDIA	INDONESIA	KENYA	KYRGYZSTAN
National treatment guidelines reflect WHO drug-resistant treatment guidelines including group 5 drugs.				
If NO what drugs are not included and/or what is missing from the national guidance.			bedaquiline, thioacetazone, imipenem/cilastatin, clarithromycin	
There are guidelines on the use of the bedaquiline				
There are guidelines on the use of delamanid				
Before registration, new and repurposed drugs are available through compassionate use or expanded access programmes or any other legal mechanisms. If yes, which one of these mechanisms is in place:				
All group 2 drugs are on the national essential medicines list (EML)				
If NO, which drugs are not included.	kanamycin, capreomycin	capreomycin	capreomycin (Cm) (capreomycin (Cm) missing from the EML 2010 but is available in the market for use)	National drug registry doesnot include Km, Amk, Cm as 2nd line TB Drugs, but as broad-spectrum antibiotics
All group 3 drugs are on the national EML				 but they are being used widely
If NO, which drugs are not included	levofloxacin, gatifloxacin, moxifloxacin		levofloxacin, gatifloxacin, moxifloxacin	Ofx, Lfx are included as BSA
All group 4 drugs are on the national EML				
If NO, which drugs are not included.	Eto, Pto, Cs, PAS, Terizidone	All Group 4 drugs	ethionamide, protionamide, cycloserine, terizidone, p-aminosalicylic acid	pas, cs, eto are included, pto, terizidone are not included
All group 5 drugs are on the national EML				
If NO, which drugs are not included.	linezolid, thioacetazone, imipenem/cilastatin	linezolid, thioacetazone, bedaquiline	clofazimine, linezolid, thioacetazone, imipenem/cilastatin are not included	All (Amx/Clav included as BSA)

LEGEND  Yes  No  Not applicable

MOZAMBIQUE	NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION
			 (Under revision)	
bedaquiline; linesolide; imepenem; meropenem and clofazimine				clofazimine is not registered in RF, but it could be used in life saving conditions with special permission of MoH
				
				
		 on Compassionate		
	 but it is being updated to cover all DR-TB medicines			
	kanamycin, amikacin and capreomycin			
				
ofloxacin	All. levofloxacin, moxifloxacin, gatifloxacin			
		 Eto/Pto,Cs,PAS, available in local market		
terizidone	All: ethionamide, prothionamide cycloserine terizidone p-aminosalicylic acid p-aminosalicylic- Na	terizidone		
				
Not known	bedaquiline, delamanid, imipenem, cilastatin, thiacetazone, linezolid,	lzd, cfz, imp, mpnm	bedaquiline, delamanid, imipenem etc	clofazimine

### III. DR-TB TREATMENT REGIMENS (CONT'D)

	SOUTH AFRICA	SWAZILAND	TAJIKISTAN	UKRAINE
National treatment guidelines reflect WHO drug-resistant treatment guidelines including group 5 drugs.	●	●	●	●
If NO what drugs are not included and/or what is missing from the national guidance.	●	Although available, training and wider availability will be expanded from Sept 2015 onwards Regulation issues are also not clear	●	●
There are guidelines on the use of the bedaquiline	●	●	●	●
There are guidelines on the use of delamanid	●	●	●	●
Before registration, new and repurposed drugs are available through compassionate use or expanded access programmes or any other legal mechanisms. If yes, which one of these mechanisms is in place:	●	●	●	●
All group 2 drugs are on the national essential medicines list (EML)	●	●	●	●
If NO, which drugs are not included.	●	capreomycin	●	●
All group 3 drugs are on the national EML	●	●	●	●
If NO, which drugs are not included	●	ofloxacin	●	●
All group 4 drugs are on the national EML	●	●	●	●
If NO, which drugs are not included.	●	●	●	●
All group 5 drugs are on the national EML	●	●	●	●
If NO, which drugs are not included.	clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, clarithromycin	Not known	linezolid partners bought and clofazimine	●

LEGEND  Yes  No  Not applicable

UZBEKISTAN	VIET NAM	ZIMBABWE
	terizidone (group 4 ), thioacetazone (group 5)	
		
 In pilot region of KK	Not known	
	Not known	
		 Article 75 in the Medicines and Allied Substances Control Act Chapter 15:03
		
		kanamycin, capreomycin, amikacin
	moxifloxacin	
		All: Levofloxacin, moxifloxacin, ofloxacin
	prothionamide, terizidone	
PAS		terizidone, prothionamide
	linezolid, thioacetazone	
bedaquiline, clofazimine (registered as leprosy drugs) imipenem, linezolid, delamanid	bedaquiline, delamanid, imipenem, cilastatin, thiacetazone, linezolid,	linezolid, thioacetazone, imipenem/cilastatin, clarithromycin

# IV. MODELS OF CARE

	AFGHANISTAN	ARMENIA	BELARUS
Drug-susceptible TB (DS-TB) treatment can be started at the primary health care level			
If NO: At what level is DS-TB treatment started?			Not known
DR-TB treatment can be started and dispensed from the district level.			
If NO: At what level is DR-TB treatment started and dispensed?	Only in Afghan-Japan Communicable Diseases Hospital located in capital of the country		
Nurses or health workers other than doctors can start adults on DS-TB treatment			
Routine hospitalization is not required for the intensive phase of DS-TB			
If NO: What time period is recommended?		Until smear microscopy conversion to negative is achieved ; Two consecutive negative smear minimum 2 weeks apart	2 months
Routine hospitalization is not required for the intensive phase of DR-TB	 Required/ Yes	 There is no distinction about the hospitalization related to intensive or continuous phase. Actually, it is more related to the bacteriological status of the patient. (ei , S+ or S-)	
If NO: What time period is recommended?	Not known	Until smear microscopy conversion to negative is achieved; Two consecutive negative smear minimum 2 weeks apart. According to the protocol (D10), XDR-TB cases has to stay until the end of the intensive phase in NTC-TB hospital But it is not a practical scenario, as it means that XDR-TB patients can get treatment for intensive phase in Aps Even under CU programme (the guideline is not updated)	3-4 months
TB treatment cannot be started in health facilities providing HIV care	 Cannot be started		
HIV treatment cannot be started in health facilities providing TB care	 HIV treatment can be started in facilities providing TB care	 According to the protocol HIV treatment can be initiated and continued in TB structures ( in practice HIV specialist attends TB hospital for patient assessment and Rx initiation )	
Some health worker provides TB and HIV treatment at the PHC level			
Is ART started for all TB patients irrespective of CD4 counts?			

LEGEND  Yes  No  Not applicable

BRAZIL	CAMBODIA	CHINA	DRC	GEORGIA
	 (for smear-positive TB cases)			
	For smear-negative and extra-pulmonary: generally at hospitals.	County level		TB treatment starts at central or regional TB facility level (in-pt or out-pt, as required)
				
In Brazil, DR-TB and special scheme cases are dealt in secondary and tertiary levels.	They are started at one of about nine active MDR-TB treatment sites.	City level		
	 for smear-positive TB cases			
				
				Hospitalization time is until smear conversion and/or clinical improvement.
	 except for a few initial days to check for tolerance to the drugs			
None. Cases are hospitalized according to other criteria		The first two months of the intensive phase		Hospitalization time is until smear conversion and/or clinical improvement.
 it can				
				
	 often			
				

## IV. MODELS OF CARE (CONT'D)

	INDIA	INDONESIA	KENYA	KYRGYZSTAN
Drug-susceptible TB (DS-TB) treatment can be started at the primary health care level				
If NO: At what level is DS-TB treatment started?				At hospital and PHC
DR-TB treatment can be started and dispensed from the district level.				
If NO: At what level is DR-TB treatment started and dispensed?				In regional TB hospital
Nurses or health workers other than doctors can start adults on DS-TB treatment				
Routine hospitalization is not required for the intensive phase of DS-TB				
If NO: What time period is recommended?				Until smear conversion
Routine hospitalization is not required for the intensive phase of DR-TB	 it is required	 not recommended		Not known
If NO: What time period is recommended?	Approx. 15 days			Not known
TB treatment cannot be started in health facilities providing HIV care				
HIV treatment cannot be started in health facilities providing TB care				 HIV treatment can be started at TB centre with visit of HIV specialists
Same health worker provides TB and HIV treatment at the PHC level				 nurses do both
Is ART started for all TB patients irrespective of CD4 counts?				

LEGEND  Yes  No  Not applicable

MOZAMBIQUE	NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION
				
				In TBD, after decision of central region TB medical committee
				 but only as an exclusion decision of TB committee
		Treatment is started only at PMDT treatment sites level and treatment is dispensed on monthly basis from these sites and patients are treated through ambulatory care	Secondary level facility province hospital	Mostly in Central Regional TBD
				 only TB doctors
				 but it depends on individual situation of the patient and decision of TB committee
				Until smear conversion
				 Depends on individual situation of the patient and decision of TB committee
			Not yet standardized country-wide	Until culture conversion
			Not yet but discussed as part of the TB/HIV collaboration	
			Not yet in TB facilities but is being discussed as part of TB/HIV collaboration	 HIV treatment can be started in health facilities providing TB care after getting recommendation from HIV specialist
	No referral is made to HIV sites			 but TB doctor has to coordinate all ART with HIV specialist
	 for all patients that are HIV+	 Only given to patient with CD4 count < 400		

## IV. MODELS OF CARE (CONT'D)

	SOUTH AFRICA	SWAZILAND	TAJKISTAN	UKRAINE
Drug-susceptible TB (DS-TB) treatment can be started at the primary health care level	●	●	●	●
If NO: At what level is DS-TB treatment started?	●	●	●	DSTB treatment starts at the special TB facility (TB clinic, TB dispensary, TB cabinets)
DR-TB treatment can be started and dispensed from the district level.	●	●	● Only after confirmation of diagnosis by the TB Council (there are national and oblast level TB councils) . SL TB drugs are available in all districts	● If district is what we call in Ukraine Oblast. / province level ● If district is what we call Rayon (a district within an oblast)
If NO: At what level is DR-TB treatment started and dispensed?	●	●	●	DR TB treatment can be started at specialized TB hospitals (Oblast TB Dispensaries)
Nurses or health workers other than doctors can start adults on DS-TB treatment	●	●	●	●
Routine hospitalization is not required for the intensive phase of DS-TB	●	●	● not required. Certain criteria for hospitalization of DR-TB identified in the National TB Guideline. In the rest of the cases – ambulatory treatment	●
If NO: What time period is recommended?	●	●	●	●
Routine hospitalization is not required for the intensive phase of DR-TB	●	●	● not required Certain criteria for hospitalization of MDR-TB identified in the National MDR -TB Guideline. In the rest cases – ambulatory treatment	● not required
If NO: What time period is recommended?	For MDR-TB patients hospitalization of patients until they are confirmed to be non-infectious. For XDR-TB patients, the duration of stay in the hospital may vary from patient to patient depending on the clinical response to treatment, on average it is six months.	●	Not known	●
TB treatment cannot be started in health facilities providing HIV care	●	●	●	●
HIV treatment cannot be started in health facilities providing TB care	Not known	Not known	●	●
Same health worker provides TB and HIV treatment at the PHC level	Not known	●	●	●
Is ART started for all TB patients irrespective of CD4 counts?	●	●	● if both diagnoses confirmed	●

LEGEND  Yes  No  Not applicable

UZBEKISTAN	VIET NAM	ZIMBABWE
		
District / rayon level		
	Only at provincial sites and in the process of decentralization to district level.	
State level /Oblast level		
		
		
2 months		
		
	As per PMDT guidelines in Viet Nam, MDR-TB treatment begins with an inpatient treatment phase for about 15 days and discharged when patient is stable and meets other PMDT requirements.	
		
 It can be started but only by HIV specialists		 it can be started
		
		

# V. DRUG REGULATORY ENVIRONMENT

	AFGHANISTAN	ARMENIA	BELARUS	BRAZIL
There is a process for accelerated registration of DR-TB drugs, including new TB drugs				
What drugs registered in-country? Please state which drugs in a group are NOT registered.	All drugs used for treatment of MDR-TB (standard treatment)	inh, pyrazinamide, ethambutol, rifabutin are not registered. rifampicin, tubertam registered	Not known	Non-registered drugs: group 2- kanamycin and capreomycin; group 4- PAS, cycloserine and prothionamide; group 5- clofazimine and thioacetazone
All group 1 drugs		 isoniazide; pyrazinamide; ethambutol tablets and rifabutin are not registered.		
All group 2 drugs				
All group 3 drugs				
All group 4 drugs	eto, pas and cys			
All group 5 drugs	co-amoxiclav and clarithromycin	 cClofazimine, Bdq is not registered		
A prescription is required to purchase/procure TB medicines (not over the counter)				
If NO: Which drugs can be bought without prescription.		If they are all mentioned drugs available in the pharmacy (some of them are available)		TB FLD are only available at public health service and can not be bought. Some SLD are available at drugstores but only can be purchased with doctors' prescription. The Unified Health System in Brazil (SUS) provides all SLD for TB patients free of charge. For procurement we also do not need prescription, excepted for the drugs that WHO require.
NTP procures quality-assured TB drugs according to SRA or WHO standards	 ( GDF)		 Only for 1st line drugs	

LEGEND  Yes  No  Not applicable

CAMBODIA	CHINA	DRC	GEORGIA	INDIA
				
The programme can have special waivers even if not registered.	Not known	Not known	Most of the TB drugs are registered in the country, but sources are not WHO prequalified ones. <a href="http://pharmacy.moh.gov.ge/Pages/Products.aspx">http://pharmacy.moh.gov.ge/Pages/Products.aspx</a>	All drugs are legally available.
Not known			 Except isoniazid and rifabutin	
Not known				
Not known				
Not known			 Only cycloserine registered	
Not known			 All group 5 drugs are registered except new drugs (bdq and dlm)	Not known
This is nearly zero. It is very rare to buy anti-TB drugs over the counter.			 starting from September 2014	 Not implemented widely
This is very rare based on GDF convenience-sampling surveys.			None of the TB drugs can be purchased without prescription.	Not known
	Not known			Two sources: GDF supply & GOI Procurement. All drugs procured with internal QA system extended to storage and distribution points

# V. DRUG REGULATORY ENVIRONMENT (CONT'D)

	INDONESIA	KENYA	KYRGYZSTAN	MOZAMBIQUE
There is a process for accelerated registration of DR-TB drugs, including new TB drugs			 for all WHO prequalified drugs	
What drugs registered in-country? Please state which drugs in a group are NOT registered.	Not known	Not known	None of the group 2 to group 5 are registered to be used in TB	Not known
All group 1 drugs			Not known	
All group 2 drugs	 Capreomycin		Not known	 amikacin; capreomicin
All group 3 drugs	 All registered in the country	 gatifloxacin	Not known	 moxifloxacin; gatifloxacin
All group 4 drugs	 All group 4 are not registered	 protonamide, terizidone p-aminosalicylic acid	Not known	 etionamide; protonamide; cycloserine; terizidone, pas
All group 5 drugs	 linezolid, thioacetazone, bedaquiline	 Group 5 clofazimine, bedaquiline	Not known	 bedaquiline and delamanid are also not included
A prescription is required to purchase/procure TB medicines (not over the counter)				
If NO: Which drugs can be bought without prescription.			You can buy any drug over the counter without prescription	
NTP procures quality-assured TB drugs according to SRA or WHO standards			 through GDF mainly for 2nd line and 3rd line drugs	 WHO (GDF)

LEGEND  Yes  No  Not applicable

NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION	SOUTH AFRICA
 Prescription is as per National TB Manual based on the weight of the patient guideline		 National Medicines Policy	 bedaquiline is already registered	
Not known	Not known	All drugs in current treatment are registered except new drugs, which are not registered	clofazimine is not registered	dlm, cfz, lzd
 rifambutin				
 kanamycin, amikacin and capreomycin				Not known
 levofloxacin, moxifloxacin, gatifloxacin				Not known
 ethionamide, prothionamide cycloserine terizidone p-aminosalicylic acid p-aminosalicylic- na	terizidone			Not known
 bedaquiline, delamanid, imipenem, cilastatin,thiacetazone, linezolid,	lzd, cfz, imp, mpnm		 clofazimine is not registered in RF	Not known
				Not known
None			Mostly all drugs, including all TB drugs and other antibiotics can be bought without prescription. Only, for example, psychotropic drugs and strong pain killers need prescriptions.	Not known
			 among all TB drugs produced in RF, only cycloserine is approved by WHO standards	Not known

# V. DRUG REGULATORY ENVIRONMENT (CONT'D)

	SWAZILAND	TAJKISTAN	UKRAINE	UZBEKISTAN
There is a process for accelerated registration of DR-TB drugs, including new TB drugs				
What drugs registered in-country? Please state which drugs in a group are NOT registered.	Not known	RH 150/150 and 150/75 (LUPIN); - the registration will expire in 2016 For the rest drugs was expired in 2015: E100 (Fatoll), H 100 (McLeods), Z 150 (Lupin), RH 60/30, 60/60 (mcleods) and RHZ 60/30/150 (McLeods)	Not known	Not known
All group 1 drugs		Not known		
All group 2 drugs		Not known		
All group 3 drugs		Not known		
All group 4 drugs		Not known		
All group 5 drugs		Not known		
A prescription is required to purchase/procure TB medicines (not over the counter)				 but not always followed
If NO: Which drugs can be bought without prescription.			Not known	1st-line TB drugs ; 2nd-line TB drugs; linezolid and moxi also possible
NTP procures quality-assured TB drugs according to SRA or WHO standards		 Since 2005 NTP procures TB drugs through GDF using GF funds		

**LEGEND**  Yes  No  Not applicable

VIET NAM	ZIMBABWE
	
	The TB drugs used by the NTP are included in the essential drug list of Viet Nam and TB drugs are exempt from registration and import licensing. Furthermore, national programmes (including the NTP) are not required to register the drugs they use.
	
	 capreomycin not registered
	 moxifloxacin and ofloxacin not registered
	 para-amino salicylic acid (pas), cycloserine, terizidone, ethionamide, prothionamide are not registered
Not known	 clofazimine, linezolid, thioacetazone, imipenem/ cilastatin, are not registered
 Only specific NTP-used anti-TB drugs (brands) restricted from purchase OTC.	
All excluding NTP-specific anti-TB drugs.	
GF will supply 1st-line in 2016; MOH will start purchasing 1st line at end of 2016 for use in 2017	 TB drugs are mainly purchased through Global Drug Facility. The Medicines Control Authority of Zimbabwe conducts analysis of all TB medicines prior to in-country distribution.

# GENEXPERT PLACEMENT SUMMARY

	Provide total number of GeneXpert devices implemented in the country (in the public sector). Specify number of devices within each category: 2-modules devices; 4- modules; 8- modules; 16-modules; 32 modules, etc	Please specify the number of GeneXpert devices implemented at the different levels of the laboratory network
<b>AFGHANISTAN</b>	Only 2 GeneXpert machines are available in the country (1 in NRL and 1 in FMIC (private sector), that one in the NRL is 8-model and the one is available French Medical Institute for children (FMIC) model is not clear with us. (what is the full form of FMIC)	Only 2 GeneXpert machines are available in the country (1 in NRL and 1 in FMIC Hospital (private sector))
<b>ARMENIA</b>	4 devices available. Under new GF grant; the National TB programme will receive 13 new Xpert MTB/ RIF devices (3 with 4 modules and 10 with 2 modules)	Reference laboratory: 2 specialized hospitals: 1 district level / subdistrict level: 1 Microscopy centre level: 0 Community outreach or mobile clinics: 0
<b>BELARUS</b>	15 total devices; 2- and 4-modules devices	Reference laboratory: 1 specialized hospitals: 0 district level or regional: 6 subdistrict level: 7 Microscopy centre level: 0 Community outreach or mobile clinics: 0 Penitentiary: 1
<b>BRAZIL</b>	175 machines of 4 modules	Reference laboratory: 05 specialized hospitals: 26 district level / subdistrict level: 17 microscopy centre level: 126 community outreach or mobile clinics: 1
<b>CAMBODIA</b>	Not known	Not known
<b>CHINA</b>	Not known	Reference laboratory : 372 +160; Specialized hospitals: 340 +16
<b>DRC</b>	41 nationwide ; 2 modules :25; 4 modules:16	Reference laboratory: 1 specialized hospitals: 0 district level / subdistrict level: 11 microscopy centre level: 29 community outreach or mobile clinics: 0
<b>GEORGIA</b>	16 devices in total, all of them 4-modules.	Reference laboratory: 4 specialized hospitals: 0 district level / subdistrict level: n/a microscopy centre level: 10 community outreach or mobile clinics: Prison microscopy lab: 2
<b>INDIA</b>	89 by end 2014 +30 (supposed to be put in place in march '15) 4 modules	Plans to cover all districts by end 2017 (950 devices)
<b>INDONESIA</b>	43 GX 4-module machines	Reference laboratory: 4 specialized hospitals: 39 district level / subdistrict level: NA microscopy centre level: NA community outreach or mobile clinics: NA
<b>KENYA</b>	2 modules – 2 4 modules – 70 8 modules – 0 16 modules – 1 32 modules – 0	Reference laboratory: 1 specialized hospitals: 3 district level / subdistrict level: 69
<b>KYRGYZSTAN</b>	Total 8 GeneXpert machines with 4 modules each	Total 8 Prison sector -1 Kara-Suu district Hospital- 1 FMC Issykata – 1 Sokuluk FMC - 1 CTBD Bishkek – 1 Batken oblast TB centre - 1 Talas oblast TB centre – 1 Osh city TB centre - 1
<b>MOZAMBIQUE</b>	36 GeneXperts 4-module devices	Reference laboratory: 3 specialized hospitals: 2 district level / subdistrict level: 31

	Provide total number of GeneXpert devices implemented in the country (in the public sector). Specify number of devices within each category: 2-modules devices; 4- modules; 8- modules; 16-modules; 32 modules, etc	Please specify the number of GeneXpert devices implemented at the different levels of the laboratory network
<b>NIGERIA</b>	131; all 4-module devices	6 Reference Laboratories ( 2 National Reference Lab. and 4 Zonal Reference Lab)
<b>PAKISTAN</b>	42 (June 2015) - One 16-module and All other 4-module	Reference laboratory: NRL: 16 module SPRLs - 5 specialized hospitals: PMDT treatment sites: 18 district level / subdistrict level: 18 microscopy centre level: NIL community outreach or mobile clinics: NIL
<b>PNG</b>	21 (4 modules)	Reference laboratory and district level hospital
<b>RUSSIAN FEDERATION</b>	73 GeneXpert devices implemented in the country (in the public sector). No data about number of modules.	Not known
<b>SOUTH AFRICA</b>	in 2014*1294 instruments in 207 sites	Not known
<b>SWAZILAND</b>	38 (Sept 2015) All 4-module, except 1 16-module in the Mbabane Government Hospital Laboratory	Reference laboratory: specialized hospitals: District Hospitals: 9 Health Centres (subdistrict): 5 Clinics: 3 NGOs: 6 ? Private: 5 Some of the facilities have 2 units of 4 modules
<b>TAJKISTAN</b>	15; 2-module devices – 1pcs; 4- module devices -14pcs.	National Reference laboratory –One GX device with 2 modules; National TB center microscopy laboratory -2 GX devices with 4 modules; Regional TB centers -3 GX device with 4 modules; Children TB hospital –one GX device wit 4 modules; District level microscopy center level -8 GX devices with 4 modules.
<b>UKRAINE</b>	There 30 G/Xpert in Ukraine: 28 -4-module 1 – 2-module devices. In addition to this GF bought 10 more 4-module devices. In the prison sector: 8 – 4 module devices. 10 - 4- module devices. All devices procured under GF are in the process of installation	NRL: 1 G/Xpert; 3rd level lab – 29 (3 HIX 28 G/Xperts 4-module device and 1 G/Xpert 1-module device ); 3rd level prison labs 8 (G/Xpert 4-module device in each lab); 2nd level labs - 3 (2 G/Xpert 4-module device, 1 G/Xpert 1 module device). 7 - 1st lab level (AIDS centre) G/Xpert 4-module device in each lab. in process of installation 3 G/Xpert 4-module device B Cl3O.
<b>UZBEKISTAN</b>	Total: 25 in the country Karakalpakstan: 6 plus 2 in the pipeline Rest of Uzbekistan: 19	Karakalpakstan: 5 - central level, 1 - district. By the end of 2015: 5 - central, 3 - district Tashkent: National AIDS centres: 2 NRL: 2 Oblast (state level) and Rayon level: 15
<b>VIET NAM</b>	32 machines of which 30 for public use as per National Strategic Plan drafted in mid-2014, but 46 Xpert machines mentioned as recently as December 2014. (According to the 20.20130419 WHO PMDT Monitoring Mission Report, 2012 7 sites, 2013-17 sites and 2004-15 -43 Xpert sites A total of 43 Xpert machines to be installed between 2013 and 2015 Page 22).	Estimate based on 2013 GLC report. Reference laboratory: 6 (National Lung Hospital, Pham Ngoc Thach Hospital) specialized hospitals: 37 (Central TB hospitals K71 & K74, Hanoi Lung Hospital, other provincial lung disease and TB hospitals and MDR-TB treatment sites, etc.) district level / subdistrict level: 6 (3 at DTU's in Hanoi and HCMC each) microscopy centre level: 0 (likely included above) community outreach or mobile clinics: 0 ( Page 22, 20.20130419 WHO PMDT Monitoring Mission report)
<b>ZIMBABWE</b>	96 (GX-4 = 93, GX-16= 3)	Reference laboratory: 2 Specialized hospitals: 3 Provincial Hospitals (including 2 major city hospital): 10 District level / subdistrict level: 71 microscopy centre level: 8 community outreach or mobile clinics: 2



"We would like to thank the MSF field teams, Stop TB Partnership members, and NTPs in the 24 countries who have provided us with the information on which this survey is based. We would also like to acknowledge the contribution of Dr. Daisy Lekharu as lead analyst and writer of the report."

**Design: Missing Element Prague**

Disclaimer: Clinical decisions should not be made based on this document. Stop TB Partnership and MSF have made every effort to ensure the accuracy of the data in this report, but we make no representations or warranties, either expressed or implied, as to their accuracy, completeness or fitness for a particular purpose.

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