OUT OF STEP 2015

TB POLICIES IN 24 COUNTRIES

A survey of diagnostic and treatment practices

MEDECINS SANS FRONTIERES

Stop TB Partnership

ABOUT MÉDECINS SANS FRONTIÈRES

Médecins Sans Frontières (MSF) is an independent international medical humanitarian organisation 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 organisation is now one of the largest NGO treatment providers for drug-resistant TB. In 2014, the organisation started 21,500 patients on first-line TB treatment across projects in more than 20 countries, with 1,800 patients on treatment for 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 1,400 partners are a collective force that is transforming the fight against TB in more than 100 countries. They include international and technical organisations, 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

Optimised TB Policies: Crucial Steps to Ending TB

This year marks a crucial crossroad 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 Organisation'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 realise 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; multidrug-resistant TB (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 four 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 recognise 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

Pierre-Yves Bernard/MSF

Purpose

This 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 TB (DS-TB), treatment of drug-resistant TB (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 Organisation (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 National Tuberculosis Programme (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; these included Armenia, Belarus, Kenya, Kyrgyzstan, Russian Federation, Swaziland, Uzbekistan and Viet Nam.

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'.

Sami Siva

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[1] and The Global Plan to End TB 2016-2020[2], 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[3].
- Only five countries have recommended Xpert MTB/RIF to be used for paediatric TB diagnosis, and only four have recommended the use of Xpert MTB/RIF for extra-pulmonary tuberculosis (EPTB) patients.
- Countries need to reduce significant gaps in the 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 implementation status of WHO's recommendation on the use of rapid molecular tests as the initial diagnostic test (either for all TB cases or only for high-risk groups). We found that 15 out of 24 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 fixed-dose combinations (FDCs) for daily treatment and the recommendations of the International Standards of TB care, these should be replaced by daily treatment.
- Ten countries are in line with WHO guidance from 2010[4], 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[5], and only three countries do not have 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 List (EML) and are in line with the WHO Model List of Essential Medicines[6].
- 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 Former Soviet Union (FSU) region.
- Fifteen 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. Democratic Republic of Congo
8. Georgia
9. India
10. Indonesia
11. Kenya
12. Kyrgyzstan
13. Mozambique
14. Nigeria
15. Pakistan
16. Papua New Guinea
17. Russian Federation
18. South Africa
19. Swaziland
20. Tajikistan
21. Ukraine
22. Uzbekistan
23. Viet Nam
24. Zimbabwe


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MODELS OF CARE

- Seventeen countries have decentralised 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 hospitalisation as part of their guidance for the treatment of DR-TB. In countries with compulsory hospitalisation in their guidance, the duration of hospitalisation 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 three billion and a combined GDP of US$16 trillion. The BRICS countries also account for 46% of all cases of TB and 40% of all TB-related mortality.[7] As such, these countries have the power to drastically reduce the global TB burden through joint cooperation and shared approaches.[8]

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 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 testing 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 treatment for DS-TB, instead of daily treatment.
- FDCs are still not the recommended formulation in India or the 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 drugs in Groups 2-5 on the national EML: Russian Federation and South Africa include all drugs in Groups 2,3 and 4; Brazil includes all drugs in Group 3; and India includes none.
- India, Russian Federation 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 decentralisation 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 hospitalisation 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[3], including recommending rapid molecular testing (e.g., Xpert MTB/RIF) as the initial diagnostic 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[9]. 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[10]. 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[11]. 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[12]. 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 decentralised 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)[13,14].

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 8 of the 24 countries surveyed (33%) 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 (e.g., Xpert MTB/RIF) as the initial test for all presumptive TB cases	Countries that recommend rapid molecular tests as the initial test only for high-risk groups
Belarus	Afghanistan
Brazil (subnational)	Cambodia
Georgia	Democratic Republic of Congo
Russian Federation	India
South Africa	Indonesia
Swaziland (implemented widely, but with technology stock-outs)	Kenya
Tajikistan (subnational)	Kyrgyzstan
Ukraine (not widely; only at oblast level)	Mozambique
	Nigeria
	Pakistan
	Papua New Guinea
	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 6 out of the 8 countries that recommend rapid molecular testing as the initial diagnostic test for all presumptive TB cases (namely, Belarus, Brazil, Georgia, Russian Federation, Tajikistan and Ukraine), 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 Afghanistan, Cambodia, Democratic Republic of Congo [DRC], India, Indonesia, Kenya, Kyrgyzstan, Mozambique, Nigeria, Pakistan, Papua New Guinea [PNG], Uzbekistan, Viet Nam and Zimbabwe.) have recommended the use of rapid molecular-based testing (e.g., Xpert MTB/RIF) 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 page 27 '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).

Matthew Smeal/MSF

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) in adult population	Paediatric TB	EPTB	Smear negative
Afghanistan, Belarus, Brazil, Cambodia, DRC, Georgia, India, Indonesia, Kenya, Kyrgyzstan, Mozambique, Nigeria, Pakistan, PNG, Russian Federation, South Africa, Swaziland, Tajikistan, Uzbekistan (TB/HIV coinfected), Ukraine, Viet Nam, Zimbabwe	India, Kyrgyzstan, Nigeria, Viet Nam, Zimbabwe	India, Nigeria Pakistan, Viet Nam	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 Georgia, Kyrgyzstan and Viet Nam, reported that they recommend rapid molecular testing (e.g., Xpert MTB/RIF) for the purpose of testing or screening for drug resistance and for people with a confirmed TB diagnosis.

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 24 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 sputum 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 the 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 the 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 page 27 'Diagnostics Implementation Summary').

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 decentralisation of DR-TB diagnosis. By contrast, most of the devices in Armenia, China, Indonesia and Viet Nam 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 (no. of devices)	Specialised hospital (no. of devices)	District level/ subdistrict level (no. of devices)	Microscopy centre level (no. of devices	Community outreach or mobile clinics (no. of devices)	Remarks from countries
Afghanistan	● (1)	● (1)				2 machines available (1 at NRL and 1 at a 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/prisons (2)
India	● (4 at NRL; 18 at IRL)	● (35)	● (62+2)			Plans to cover all districts by end of 2017 (950 devices)
Indonesia	● (6)	● (39)	-	-	-	
Kenya	● (1)	● (3)	● (69)	-	-	
Kyrgyzstan	●	●	●	-	-	Sokuluk Family Medicine Centre (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 of 131 devices implemented has been reported, but complete information on placement is not available
Pakistan	● (6)	-	● (36)	-	-	
PNG	●	-	●	-	-	And at 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 a few public-private mix (PPM) sites
Tajikistan	● (6)	● (1)	● (8)	-	-	
Ukraine	● (1)		●			NRL: 1 3rd level lab: 29 (28 4-module devices and 1 1-module device) 3rd level prison labs: 8 (1 4-module device in each lab) 2nd level labs: 3 (2 4-module devices, 1 1-module device) 1st level lab (AIDS center): 7 (1 4-module device in each lab) In process of installation: 3 4-module devices
Uzbekistan	●	-	●	-	-	Karakalpakstan: 5 at central level, 1 at district level; By the end of 2015: 5 at central level, 3 at district level 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)

Andrea Bussotti/MSF

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 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: Belarus, Georgia, Kyrgyzstan, Russian Federation, South Africa, Tajikistan and Ukraine.

All countries included in the survey reported that their national guidelines recommend second-line DST for all rifampicin-resistant TB (RR-TB), polydrug-resistant TB (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

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 treatment[4] wherever feasible with a high grade of evidence[15,16]. The recommendations note that intermittent treatment (three times per week), although not ideal, can be used during the continuation phase if each dose is directly observed.

Six out of the 24 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 treatment is still recommended.

A recent study in India[17] showed that within the intermittent treatment group there was a higher rate of people lost to follow up, which carries the associated risk of resistance generation. Although India continues to recommend intermittent treatment, the NTP reported that daily treatment will be rolled out in 104 districts in 2016, and since March 2015, pilot projects looking at daily treatments have been initiated in 30 high workload antiretroviral therapy centres for people coinfected 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[4], 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[7]. Increased levels of streptomycin resistance have been found in China[18] India[19,20] Mozambique[21], Uzbekistan[22] and Viet Nam[23] where the Category II regimen is still recommended.

Ten of the 24 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 3 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 (FDCs)

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[24]. 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)[25] state that "fixed-dose combinations (FDCs) are desirable as they simplify drug procurement and logistics, the delivery of directly-observed treatment (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 for children were increased in 2010 and further updates were made in the latest WHO paediatric TB guidelines[26]. The good news is that five years following the interim recommendation on the paediatric first-line drug dosages, only three countries (Swaziland, Ukraine and Viet Nam; the status of Ukraine and Viet Nam are not known) have yet to update their guidance on the doses required for the first-line 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, 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, Belarus, Georgia, India, Mozambique, Pakistan, Tajikistan and Uzbekistan), 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 WHO Essential Medicine List.
- Drugs categorised 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 individualised approach that compiles a regimen using drugs that the patient is sensitive to from the five groups or classes of drugs.

Table 3: 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, rifapentine
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 recognised 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[27]. Only 3 of the 24 countries have all the drugs from Groups 1, 2, 3, 4 and 5 on their national EML lists (Belarus, Cambodia 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, 5 countries had just 1 complete group of drugs on their national EML, 4 countries had just 2 complete groups, and 5 countries had 3 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[28]. The second drug, delamanid (Otsuka), received approval from the European Medicines Agency (EMA) and Japan's Pharmaceuticals Medical Devices Agency (PMDA) in 2014[29]. 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[30,31,32].

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 an additional three countries using bedaquiline in pilot 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 FSU region (i.e., Belarus, Georgia, Kyrgyzstan and Tajikistan). 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 extensively drug-resistant (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

- Decentralisation 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 hospitalisation 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 prioritised; 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[33]. In order to improve adherence, infection control and ensure the minimal disruption to patients, TB services should be decentralised 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[34,35,36]. Seventeen out of 24 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 decentralisation of DS-TB care is to allow nurses to initiate treatment. This approach has been formalised 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[37]. The challenges regarding health care worker (HCW) shortages are also present for TB[38], 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 African 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 decentralisation of DS-TB services and all the benefits that confers on patients.

Countries where nurses/HCWs can start adults on DS-TB treatment:
Brazil, Cambodia (for smear + cases), DRC, Georgia, Kenya, Mozambique, Nigeria, PNG, South Africa, Swaziland, Viet Nam and Zimbabwe.

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
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 ?
Belarus	Status not known
China	Country level (reported by NTP response)
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
Kyrgyzstan	Status not known
Russian Federation	After decision of central region TB medical committee
Ukraine	According to Order No. 620 (Consolidated TB protocol), patients with pulmonary tuberculosis with positive sputum smear by bacterioscopy method have to be hospitalised (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
Uzbekistan	TB treatment is initiated at the district/rayon level

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 hospitalisation[39]. WHO has recommended ambulatory models of care[40], and decentralisation of DR-TB services could have significant impact on the total cost of treating MDR-TB. Decentralisation has not been associated with poorer outcomes[41,42,43], and is associated with decreased rates of people lost to follow up [44] and lower costs.[45,46,47]

The process of decentralising DR-TB services is not as straightforward as for DS-TB, as DR-TB patients may be more likely to require hospitalisation 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 hospitalisation only be recommended based on the clinical condition of the patient and not routinely recommended or made compulsory. Treatment initiation can still be decentralised 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 FSU region (Armenia, Georgia, Russian Federation, Tajikistan and Uzbekistan), 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 hospitalisation for DR-TB patients, thus weakening the potential advantages of decentralising treatment initiation. More than half of the countries surveyed do not include routine hospitalisation as part of their guidance for the treatment of DR-TB. In countries with compulsory hospitalisation in their guidance, the duration of hospitalisation 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[48] associated with hospitalisation. (Please refer to Table 6 for the duration of hospitalisations.)

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 hospitalising 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 hospitalisation is no longer required for the intensive phase of DS-TB. The decision to hospitalise 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 hospitalisation for DR-TB (although this was not required for DS-TB patients). This policy shift away from routine hospitalisation 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 decentralisation of TB care.

Countries that DO NOT RECOMMEND routine hospitalisation for the treatment of DR-TB (15/24)
Brazil, Cambodia*, DRC, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, PNG, Russian Federation*, Swaziland, Tajikistan, Ukraine, Uzbekistan*, Zimbabwe

*Notes:

Russian Federation: depends on the individual patient's situation (Order of MOH RF #951 from 29/12/2014)

Cambodia: a few days may be required initially to check the tolerance of drugs

Uzbekistan: Prikaz No 383, MOH (24 October 2014)

Table 6: Duration of hospitalisation for DR-TB treatment

Country	Duration of hospitalisation
Afghanistan	Not known
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
Belarus	Three to four months
China	The first two months of the intensive phase
Georgia	Approximately 15 days
India	Hospitalisation time is until smear conversion and/or clinical improvement
Kyrgyzstan	Not known
South Africa	MDR-TB patients are hospitalised 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
Viet Nam	As per Programmatic Management of Drug-resistant TB (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

There is a strong regional trend with regard to a more centralised system in the countries in the Commonwealth of Independent States (CIS)[49]; these countries are more likely to require compulsory hospitalisation (four out of seven for MDR-TB). In addition, these countries tend towards a centralised approach to physician-initiated treatment, with four out of seven of these countries requiring doctors to initiate DS-TB treatment. This centralisation is likely due to the models of financing operating in the region[50]. However, Russia and Uzbekistan's policy changes with regard to hospitalisation indicates that the policy can be changed in a centralised 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 coinfected 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 coinfected patients is usually due to complications from overwhelming TB disease or impaired immunity from advancing AIDS. Evidence has shown that early antiretroviral treatment (ART) initiation improves outcomes[51,52]. 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/μL) should start ART within two weeks of starting TB treatment[53].

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 coinfected 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 coinfected 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/μL who were referred from TB services to separate HIV services started ART within four weeks of their TB diagnosis.[54]

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 antiretrovirals (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.[55] Decentralising TB/HIV care is also associated with better outcomes[56,57,58]. When TB services are decentralised, 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)	Countries that recommend initiation of HIV treatment in facilities providing TB care (18/24)
Belarus, Brazil, China, DRC, Georgia, India, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, South Africa, Swaziland, Tajikistan, Ukraine, Viet Nam, Zimbabwe	Afghanistan, Armenia, Belarus, China, DRC, Georgia, Indonesia, Kenya, Kyrgyzstan, Nigeria, PNG, Russian Federation, Swaziland, Tajikistan, Uzbekistan, Ukraine, Viet Nam, Zimbabwe

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 have an accelerated approval mechanism in place that allows swift registration of DR-TB medicines including new drugs[59]. Countries should participate in the collaborative registration procedure set by the WHO Prequalification of Medicines Programme (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 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[6] 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 harmonisation 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 Organisation (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 MTB/RIF 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 MTB/RIF 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 16,224 presumptive TB individuals attending health facility outpatient departments

underwent TB sputum microscopy. Of these, 7,551 HIV-positive patients who were presumed to have TB were tested using the Xpert MTB/RIF test. Xpert MTB/RIF found a total of 1,043 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 MTB/RIF 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 MTB/RIF, of which 1,494 were found to be positive for TB.

The NTLP Strategic Plan 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 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[60]. 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 formalise 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-resistant TB regimen that lasts two years.

Table 7: 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 with Janssen to access bedaquiline 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 Stop TB Partnership Global Drug Facility (GDF)
November 2015	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.

DECENTRALISATION OF DIAGNOSIS AND TREATMENT OF DR-TB

Khayelitsha, South Africa

In South Africa, tuberculosis, 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 decentralised model of care whereby DR-TB patient care and support was made available at the primary health care level. The decentralised 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 decentralised 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 decentralisation of services. Crucially, costing studies have determined that a fully decentralised DR-TB model of care costs 42% less than a centralised hospital model.

In the Khayelitsha model, decentralisation 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, and particularly multidrug-resistant tuberculosis, 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 hospitalisation in centralised 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 centralised services easily. In order to facilitate the decentralisation 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 one. The time from diagnosis to commencing treatment has been reduced, and there are no longer waiting lists for hospitalisation.

COUNTRY PERCEPTIONS ON THE IMPLEMENTATION OF THE NEW MULTIDRUG-RESISTANT TB MEDICINES

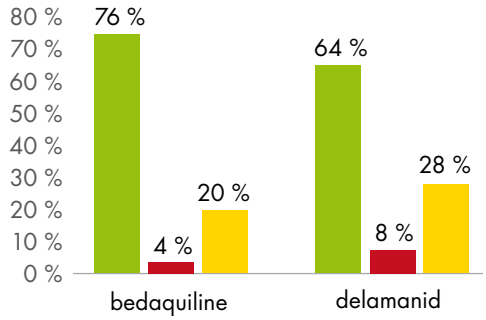
The current treatment for drug-resistant TB is long, complex, and associated with severe and life-threatening side effects. Furthermore, the treatment only has successful outcomes for approximately 50% of people who start treatment. WHO has issued interim guidance on the use[61] of two new drugs registered for use in treating multidrug-resistant 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 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% had 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 though 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.

Would countries recommend the use of new medicines?



A NEW APPROACH TO MDR-TB TREATMENT

Access to diagnosis and treatment of MDR-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, 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 an Xpert MTB/RIF test 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. It reduces the injection phase to 4–6 months, cuts the total number of tablets, and lowers the cost from around US$3,418 to $456 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[62] 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[63] 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 five 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 PAEDIATRIC FDCS: KENYA EXPERIENCE

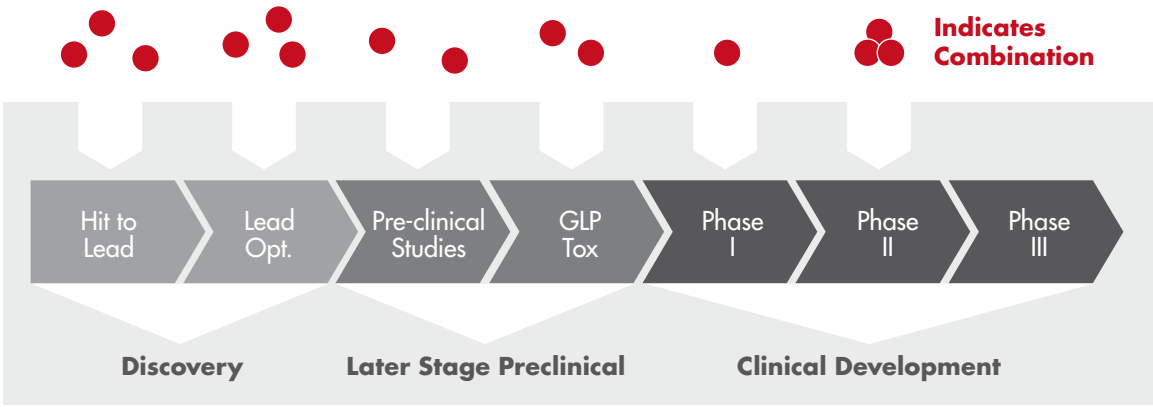
The treatment course for drug-susceptible TB (DS-TB) in children has the same drugs as used for adults, but recent changes in the doses of these medications has resulted in the current fixed-dose combination (FDC) tablets being no longer appropriate. WHO issued interim guidance in 2010 on the increased 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 in requesting the manufacturer of one of the new approved FDCs to commence the product registration process with the Kenyan drug regulatory authority. The registration process should be finalised 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 memo 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).



Legend

- Various TB Compounds
- Milestone Prize
- Grant funding

Discretionary grant funding throughout the drug development process

Large Milestone Prize for compounds entering the pool for clinical development (Phase I)

Grant funding for regimen trials (phases I – III) from existing and new sources

For more information, please visit msfaccess.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 capitalise 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 national policies are in line with international guidance.

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 decentralised and integrated care for DR-TB and DS-TB.
- Remove policies of compulsory hospitalisation for TB patients, and have hospitalisation 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 compassionate use as soon as possible. There should be parallel efforts to register new drugs so that they are available for programmatic use and 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 recognise market authorisations granted by stringent NMRAs for priority medicines.
- Implement the necessary legislation for CU as soon as possible. There should be parallel efforts to register new drugs so that they are available for programmatic use to more patients, and so that a sustainable supply can be set up.

MANUFACTURERS

Prepare for scale-up of new treatments:

- Provide access to innovative TB medicines through compassionate use.
- 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 decentralised 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 decentralised 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 ORGANISATION

- 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

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

GLOSSARY AND ABBREVIATIONS

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 authorised 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.

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

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$1,045 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$1,045 but less than US$4,125 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 Harmonisation (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 EU Regulation (EC9 No. 726/2004) or US 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$4,125 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

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

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ANNEXES

I. DIAGNOSIS

	AFGHANISTAN	ARMENIA	BELARUS	BRAZIL
Rapid molecular diagnostics (i.e Xpert MTB/RIF) are recommended as the initial diagnostic test for all adults 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 questions 1, 2 and 3 are WHO-approved or not WHO-approved	WHO-approved	WHO-approved	WHO-approved	WHO-approved
IF YES to question 2 or 3: specify groups of people or TB patient groups for whom guidelines recommend Xpert MTB/RIF	Routine culture, Xpert MTB/RIF and DST is recommended for the following groups: failed Category I or II treatment; failed anti-TB treatment in the private sector; MDR-TB contact; exposure to an institution that has 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	Every person with TB symptoms and a smear-negative test result	Diagnosed TB patients for drug resistance; initial diagnostic test for adults and children at risk of DR-TB and HIV-associated TB (high-risk groups)	Re-treatment cases; HIV-positive people; prisoners; homeless people; health professionals; indigenous populations; failure of first-line treatment; smear positive in second month of treatment
First-line 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 groups for whom first-line DST is recommended	All RR-TB cases, to formulate second-line treatment	Everyone with TB symptoms and confirmed TB cases, either by smear microscopy or molecular tests, is exposed to first-line DST (after positive culture is found); implemented YES	Done routinely for all patients	All TB cases diagnosed through Xpert MTB/RIF should receive culture and DST, and mainly all people with TB symptoms with a smear microscopy diagnosis; re-treatment cases and vulnerable populations should also be sent for culture and DST.
Second-line DST (including at least fluoroquinolones and second-line injectable agents) is recommended for all RR-TB, polydrug-resistant (PDR)-TB and MDR-TB cases	●	●	●	●

LEGEND Yes No

CAMBODIA	CHINA	DRC	GEORGIA	INDIA
●	●	●	●	●
●	●	●	●	●
●	●	●	●	●
WHO-approved	WHO-approved; not WHO-approved for smear negative (people with TB symptoms) by Chinese Food and Drug Administration	WHO-approved	WHO-approved	WHO-approved
People with MDR-TB symptoms: (i) sputum non-converters; (ii) all re-treatment cases; in addition to (iii) symptomatic contacts of known DR-TB cases; and (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 cases; people with TB symptoms; cases with clinical and chest X-ray suggestive of TB but with sputum smear-negative	Everyone with TB symptoms, including adults and children	Paediatric cases; EPTB samples; people who are HIV-positive; people with presumptive DR-TB
●	●	●	●	●
Re-treatment cases; sputum non-converters (among new smear-positive patients) at months 2 or 3; symptomatic contacts of DR-TB cases; people co-infected with TB/HIV	High-risk groups: Category I treatment failure; no smear conversion at 2 months; chronic patients; MDR-TB contacts; relapse	All RR-TB cases and all primary culture-positive cases	All groups, whenever culture is positive.	Rifampicin resistance is considered as surrogate for MDR-TB eligible for second-line treatment
●	●	●	●	●

I. DIAGNOSIS (CONT'D)

	INDONESIA	KENYA	KYRGYZSTAN	MOZAMBIQUE
Rapid molecular diagnostics (i.e., Xpert MTB/RIF) are recommended as the initial diagnostic test for all adults 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 questions 1, 2 and 3 are WHO-approved or not WHO-approved	WHO-approved	WHO-approved	WHO-approved	WHO-approved
IF YES to question 2 or 3: specify groups of people or TB patient groups for whom guidelines recommend Xpert MTB/RIF	Presumptive DR-TB cases, including contacts; people living with HIV 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 re-treatment cases: a) failures b) relapses c) return after default; DR-TB contacts; smear-positive refugees; health care workers with TB diagnosis; HIV-positive smear negative; diagnosis of TB in children; TB screening for symptomatic patients for and on isoniazid preventive therapy (IPT)	Re-treatment cases; children; MDR-TB contacts; severe clinical condition; HIV-positive; unknown HIV status in high-risk setting; migrants; prisoners; ex-prisoners	Re-treatment cases; patients with MTB+ at 2 months; elderly HIV patients and other immunologically-depressed patients; diabetics; health staff; miners; prisoners; in endemic DR-TB high prevalence areas, pregnant women and children
First-line 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 groups for whom first-line DST is recommended	All RR-TB cases from all groups in row 5 above	TB patients on re-treatment; healthcare workers; symptomatic contacts of DR-TB patients; smear-negative people living with HIV; patients returning after default (re-treatment after default); lack of smear conversion at 2 months while on first-line treatment	All cases with laboratory-confirmed TB require first-line DST	People previously treated for TB; new cases that do not convert at 2 months; MDR-TB contacts; people living with HIV; 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 RR-TB, polydrug-resistant (PDR)-TB and MDR-TB cases	●	●	●	●

LEGEND Yes No

NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION	SOUTH AFRICA
●	●	●	●	●
●	●	●	●	●
●	●	●	●	●
WHO-approved	WHO-approved	WHO-approved	WHO-approved	WHO-approved
Evaluation for DR-TB: a) symptomatic contacts of DR-TB cases; b) failure of first-line treatment; c) failure to convert (smear-positive to smear-negative) after repeat smear microscopy follow-up examination at the end of month 3 of first-line treatment; d) all patients who have been previously treated for TB	All presumptive/diagnosed TB cases with a history of previous treatment; presumptive TB cases under 15 years old; people who are HIV-positive, immunecompromised or hospitalised; healthcare workers; presumptive EPTB cases; and presumptive TB cases from whom specimen is obtained through some procedures, e.g. bronchial lavage	People who have been previously treated; non-converters (at the end of 2 months); HIV-positive people; symptomatic contacts of known MDR-TB cases; health facility staff	For all (adult and children) in whom TB is presumed	TB and DR-TB contacts; non-contact, symptomatic individuals; re-treatment after relapse, failure or default
●	●	●	●	●
RR-TB patients following Xpert MTB/RIF test	All detected with RR-TB on Xpert MTB/RIF test; others at high risk of drug resistance tested with rifampicin-susceptible test on Xpert MTB/RIF	All RR-TB cases	All TB patients	All new patients
●	● For all RR-TB patients	●	●	●

I. DIAGNOSIS (CONT'D)

	SWAZILAND	TAJIKISTAN	UKRAINE
Rapid molecular diagnostics (i.e., Xpert MTB/RIF) are recommended as the initial diagnostic test for all adults 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 questions 1, 2 and 3 are WHO-approved or not WHO-approved	WHO-approved	WHO-approved	WHO-approved
IF YES to question 2 or 3: specify groups of people or TB patient groups for whom guidelines recommend Xpert MTB/RIF	Xpert MTB/RIF test is recommended for everyone with TB symptoms, including those in congregate settings (i.e., miners, 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 testing for RR-TB; MDR-TB contacts; individuals from DR-TB risk groups (e.g., treatment defaulters, contacts of a patient deceased due to TB, etc.); penitentiary detainees with symptoms of TB; patients with progressive TB; people with TB symptoms and a history of non-standard treatment; HIV-positive individuals; TB diagnosis, without data on drug resistance; everyone with TB symptoms; healthcare workers and penitentiary facility staff who have TB symptoms; migrant workers with TB symptoms; pregnant women and postpartum women with TB symptoms; sputum smear-negative 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; for TB patients who are smear-positive after 90 doses
First-line DST (including for 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 DST is recommended for all RR-TB cases and patients considered at risk of DR-TB	●
Specify patient groups for whom first-line DST is recommended	Positive Xpert MTB/RIF test result	All people with TB symptoms; relapse; treatment failure; From Koninklijke Nederlandse Centrale Vereniging (KNCV) [Royal Netherlands Association for Tuberculosis Control]: According to the National Guidelines on DR-TB, first-line DST is recommended for all detected TB patients; second-line DST (including at least fluoroquinolones and second-line injectable agents) is recommended for all RR-TB, polydrug-resistant (PDR)-TB and MDR-TB cases	New cases (Category I and III) and Category II cases (previously treated cases and relapses)
Second-line DST (including at least fluoroquinolones and second-line injectable agents) is recommended for all RR-TB, polydrug-resistant (PDR)-TB and MDR-TB cases	●	● 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
People co-infected with TB/HIV	See comments box	All HIV-positive patients with TB symptoms; all HIV-negative patients with TB symptoms and risk factors for MDR-TB; all HIV-negative patients with TB symptoms and who are sputum negative on microscopy; children with presumptive TB; all re-treatment patients; healthcare workers with TB symptoms; presumptive TB cases with a history of travel to countries with a high DR-TB burden; contacts of DR-TB patients
Karakalpakstan: All TB patients diagnosed with rapid molecular method who have a positive culture; At national level: All patients with positive smear, positive Mycobacterium tuberculosis tine test (MBTT), rifampicin–resistant and rifampicin-sensitive result by Xpert MTB/RIF, 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 with positive Xpert MTB/RIF test, but no rifampicin resistance: perform culture and follow first-line DST in DR-TB guidelines page 15
	May not be widely implemented	(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-Z-VB6)/ 16 (Lfx-Eto-Cys-Z-VB6) - For cases with frequent use of fluroquinolone, para-aminosalicylic acid is added. - For some cases with reaction or resistance to aminoglycosides, amikacin is replaced with capreomycin			kanamycin, cycloserine, prothionamide, thioacetazone, 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 drugs except ethionamide, para-aminosalicylic acid and cycloserine			cycloserine, prothionamide
All Group 5 drugs are on the national EML		imipenem, cilastatin and clarithromycin are in the EML; clofazimine, linezolid, amoxicillin/clavulanate and thioacetazone are not mentioned in the EML		
If NO, which drugs are not included?	amoxicillin/clavulanate	clofazimine, linezolid, bedaquiline		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 finalised and approved; meanwhile, WHO EML is used as a reference
			No valid Georgian National EML exists - it is in the process of being finalised and approved; meanwhile, WHO EML is used as a reference
			No valid Georgian National EML exists - it is in the process of being finalised and approved; meanwhile, WHO EML is used as a reference
			No valid Georgian National EML exists - it is in the process of being finalised and approved; meanwhile, WHO EML is used as a reference
			No valid Georgian National EML exists - it is in the process of being finalised and approved; meanwhile, WHO EML is used as a reference
		terizidone	No valid Georgian National EML exists - it is in the process of being finalised and approved; meanwhile, WHO EML is used as a reference
			No valid Georgian National EML exists - it is in the process of being finalised and approved; meanwhile, WHO EML is used as a reference
	clofazimine, linexolid, thioacetazone, imipenem/ cilastatin	linezolid	No valid Georgian National EML exists - it is in the process of being finalised 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 (capreomycin missing from the EML 2010 but is available in the market for use)	national drug registry does not include kanamycin, mikacin, or capreomycin as second-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	ofloxacin, levofloxacin are included as bovine serum albumin (BSA)
All Group 4 drugs are on the national EML	🔴	🔴	🔴	🔴
If NO, which drugs are not included?	ethionamide, prothionamide, cycloserine, para-aminosalicylic acid, terizidone	All Group 4 drugs	ethionamide, protionamide, cycloserine, terizidone, para-aminosalicylic acid	para-aminosalicylic acid, cycloserine and ethionamide are included; prothionamide and 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	All (amoxicillin/clavulanic acid included as BSA)

LEGEND Yes No Not applicable

MOZAMBIQUE	NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION
			(Under revision)	
bedaquiline, linezolid, imipenem, meropenem and clofazimine				clofazimine is not registered, but it can be used in life-threatening conditions with special permission of MoH
		compassionate use		
	EML is being updated to cover all DR-TB medicines			
	kanamycin, amikacin and capreomycin			
ofloxacin	All. levofloxacin, moxifloxacin, gatifloxacin			
		ethionamide/prothionamide, cycloserine and para-aminosalicylic acid are available in local market		
terizidone	All: ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid, para-aminosalicylic sodium	terizidone		
Not known	bedaquiline, delamanid, imipenem, cilastatin, thiacetazone, linezolid	linezolid, clofazimine, imipenem, meropenem	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 and clofazimine	●

LEGEND Yes No Not applicable

UZBEKISTAN	VIET NAM	ZIMBABWE
	terizidone (Group 4), thioacetazone (Group 5)	
Pilot in region of Karakalpakstan	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	
para-aminosalicylic acid		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 hospitalisation 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 smears a minimum of 2 weeks apart	2 months
Routine hospitalisation is not required for the intensive phase of DR-TB	 Required	 There is no distinction between hospitalisation for the intensive and continuous phases; it is more related to the bacteriological status of the patient (i.e., smear positive or smear negative)	
If NO: What time period is recommended?	Not known	Until smear microscopy conversion to negative is achieved; two consecutive negative smears a minimum of 2 weeks apart. According to the protocol (D10), XDR-TB cases have to stay until the end of the intensive phase in the National Tuberculosis Control Center (NTC), but it is not a practical scenario, even under the 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 treatment initiation)	
Same health worker provides TB and HIV treatment at the primary health care (PHC) level			
Is antiretroviral therapy (ART) started for all TB patients irrespective of CD4 count?			

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-patient or out-patient, 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			
				Hospitalisation 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 hospitalised according to other criteria		The first two months of the intensive phase		Hospitalisation 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 hospitalisation is not required for the intensive phase of DS-TB				
If NO: What time period is recommended?				Until smear conversion
Routine hospitalisation 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 primary health care (PHC) level				Nurses do both
Is antiretroviral therapy (ART) started for all TB patients irrespective of CD4 count?				

LEGEND Yes No Not applicable

MOZAMBIQUE	NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION
●	●	●	●	●
●	●	●	●	In TB department, after decision of central region TB medical committee
●	●	●	●	● But only as an exclusion decision of TB committee
●	●	Treatment is started only at Programmatic Management of Drug-resistant Tuberculosis (PMDT) sites, where treatment is dispensed on monthly basis and patients are treated through ambulatory care	Secondary level facility province hospital	Mostly in Central Regional TB department
●	●	●	●	● 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 standardised 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-positive	● Only given to patients with a CD4 count of <400	●	●

IV. MODELS OF CARE (CONT'D)

	SOUTH AFRICA	SWAZILAND	TAJIKISTAN	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?				DS-TB 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). Second-line TB drugs are available in all districts	 If 'district-level' is equivalent to oblast/province-level in Ukraine  If 'district-level' is equivalent to rayon-level (a district within an oblast) in Ukraine
If NO: At what level is DR-TB treatment started and dispensed?				DR-TB treatment can be started at specialised TB hospitals (oblast TB dispensaries)
Nurses or health workers other than doctors can start adults on DS-TB treatment				
Routine hospitalisation is not required for the intensive phase of DS-TB			 Not required: certain criteria for hospitalisation of DR-TB are identified in the National TB Guidelines; for the rest of cases, ambulatory treatment is provided	
If NO: What time period is recommended?				
Routine hospitalisation is not required for the intensive phase of DR-TB			 Not required: certain criteria for hospitalisation of MDR-TB are identified in the National MDR-TB Guidelines; for the rest of cases, ambulatory treatment is provided	 Not required
If NO: What time period is recommended?	For MDR-TB patients: hospitalisation of patients until they are confirmed to be noninfectious; for XDR-TB patients: the duration of the stay in 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 primary health care (PHC) level	Not known			
Is antiretroviral therapy (ART) started for all TB patients irrespective of CD4 count?			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 decentralisation to district level	
State level/oblast level		
2 months		
	As per Programatic Management of Drug-resistant Tuberculosis (PMDT) guidelines in Viet Nam, MDR-TB treatment begins with an inpatient treatment phase for about 15 days; the patient is discharged when stable and having met 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 are registered in the country? Please state which drugs in a group are NOT registered	All drugs used for treatment of MDR-TB (standard treatment)	isoniazid, pyrazinamide, ethambutol and rifabutin are not registered; rifampicin and tubertam are registered	Not known	Non-registered drugs: Group 2: kanamycin and capreomycin; Group 4: para-aminosalicylic acid, 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	ethionamide, para-aminosalicylic acid and cycloserine	🔴	🟡	🔴
All Group 5 drugs	amoxicillin/clavulanate and clarithromycin	🔴 clofazimine and bedaquiline are 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)	🟡	First-line TB drugs are only available from the public health service and can not be purchased; some second-line drugs are available at drugstores, but only with a doctor's prescription. The Unified Health System in Brazil (SUS) provides all second-line drugs to TB patients free of charge; for procurement, we also do not need a prescription, except for the drugs that WHO requires
NTP procures quality-assured TB drugs according to stringent regulatory authority or WHO standards	🟢 Stop TB Partnership Global Drug Facility	🟢	🟢 Only for first-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. http://pharmacy.moh.gov.ge/Pages/Products.aspx	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 (bedaquiline and delamanid)	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 Global Drug Facility convenience-sampling surveys			None of the TB drugs can be purchased without prescription	Not known
	Not known			Two sources: Global Drug Facility supply & Government of India procurement; all drugs procured with internal Quality-Assurance 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 drugs in Groups 2-5 are registered for use with 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	● No Group 4 drugs are registered	● protionamide, terizidone para-aminosalicylic acid	Not known	● etionamide, protionamide, cycloserine, terizidone, para-aminosalicylic acid
All Group 5 drugs	● linezolid, thioacetazone, bedaquiline	● clofazimine, bedaquiline	Not known	● bedaquiline, delamanid
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 a prescription	●
NTP procures quality-assured TB drugs according to stringent regulatory authority or WHO standards	●	●	● Through Global Drug Facility mainly for second-line and third-line drugs	● Global Drug Facility

LEGEND Yes No Not applicable

NIGERIA	PAKISTAN	PNG	RUSSIAN FEDERATION	SOUTH AFRICA
		National Medicines Policy	bedaquiline is already registered	
Not known	Not known	All drugs in current treatment regimen are registered; new drugs are not registered	clofazimine is not registered	delamanid, clofazimine, linezolid
rifambutin				
kanamycin, amikacin, capreomycin				Not known
levofloxacin, moxifloxacin, gatifloxacin				Not known
ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid, para-aminosalicylic sodium	terizidone			Not known
bedaquiline, delamanid, imipenem, cilastatin, thiacetazone, linezolid	linezolid, clofazimine, imipenem, meropenem		clofazimine is not registered	Not known
Prescription is as per National TB Manual based on the weight of the patient guideline				Not known
None			Most drugs, including all TB drugs and other antibiotics, can be bought without a prescription; only certain drugs, such as psychotropic drugs and strong pain killers, require prescriptions	Not known
			Among all TB drugs produced in the Russian Federation, only cycloserine is approved by WHO standards	Not known

V. DRUG REGULATORY ENVIRONMENT (CONT'D)

	SWAZILAND	TAJIKISTAN	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	For rifampicin/isoniazid 150/150 and 150/75 (Lupin), the registration will expire in 2016; for the rest, registration expired in 2015: ethambutol 100 (Fatol), isoniazid 100 (McLeods), pyrazinamide 150 (Lupin), rifampicin/isoniazid 60/30 and 60/60 (McLeods) and rifampicin/isoniazid/ pyrazinamide 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	First-line TB drugs; second-line TB drugs; linezolid and moxifloxacin also possible
NTP procures quality-assured TB drugs according to stringent regulatory authority or WHO standards	🟢	🟢 Since 2005, NTP procures TB drugs through the Global Drug Facility using GFATM 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 are not registered
	 para-aminosalicylic acid, cycloserine, terizidone, ethionamide and 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 over the counter	
All excluding NTP-specific anti-TB drugs	
GFATM will supply first-line drugs in 2016; MOH will start purchasing first-line drugs at end of 2016 for use in 2017	 TB drugs are mainly purchased through the GDF; the Medicines Control Authority of Zimbabwe conducts an 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-module, 4-module, 8-module, 16-module, 32-module, etc.	Please specify the number of GeneXpert devices implemented at the different levels of the laboratory network
AFGHANISTAN	2 devices in total: 1 8-module device at the National Reference Laboratory (NRL) and 1 at the French Medical Institute for Children [private sector] (module information unknown)	Reference laboratory: 1 French Medical Institute for Children [private sector]: 1
ARMENIA	4 devices available; Under new GFATM grant, the National TB programme will receive 13 new Xpert MTB/RIF devices (3 4-module devices and 10 2-module devices)	Reference laboratory: 2 Specialized hospitals: 1 District/subdistrict level: 1 Microscopy centre level: 0 Community outreach or mobile clinics: 0
BELARUS	15 devices in total; includes 2-module and 4-module devices	Reference laboratory: 1 Specialized hospitals: 0 District/regional level: 6 Subdistrict level: 7 Microscopy centre level: 0 Community outreach or mobile clinics: 0 Penitentiary: 1
BRAZIL	175 machines of 4 modules	Reference laboratory: 5 Specialized hospitals: 26 District/subdistrict level: 17 Microscopy centre level: 126 Community outreach or mobile clinics: 1
CAMBODIA	Not known	Not known
CHINA	Not known	Reference laboratory: 372 + 160; Specialized hospitals: 340 + 16
DEMOCRATIC REPUBLIC OF CONGO	41 devices nationwide; 25 2-module devices and 16 4-module devices	Reference laboratory: 1 Specialized hospitals: 0 District/subdistrict level: 11 Microscopy centre level: 29 Community outreach or mobile clinics: 0
GEORGIA	16 devices in total, all are 4-module devices	Reference laboratory: 4 Specialized hospitals: 0 District level/subdistrict level: n/a Microscopy centre level: 10 Community outreach or mobile clinics: 0 Prison microscopy lab: 2
INDIA	89 by end 2014 +30 were supposed to be put in place in March 2015 all are 4-module devices	Plans to cover all districts by end 2017 (950 devices)
INDONESIA	43 devices in total; all are 4-module devices	Reference laboratory: 4 Specialized hospitals: 39 District/subdistrict level: n/a microscopy centre level: n/a Community outreach or mobile clinics: n/a
KENYA	73 devices in total; 2 2-module devices; 70 4-module devices; 1 16-module device	Reference laboratory: 1 Specialized hospitals: 3 District/subdistrict level: 69
KYRGYZSTAN	8 devices in total; all are 4-module devices	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
MOZAMBIQUE	36 devices in total; all are 4-module devices	Reference laboratory: 3 Specialized hospitals: 2 District/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-module, 4-module, 8-module, 16-module, 32-module, etc.	Please specify the number of GeneXpert devices implemented at the different levels of the laboratory network
NIGERIA	131 devices in total; all 4-module devices	Reference laboratories: 6 (National Reference Laboratory: 2; Zonal Reference Laboratory: 4)
PAKISTAN	42 devices in total as of June 2015; 1 16-module device and the rest are 4-module devices	National reference laboratory: 1 Provincial reference laboratories: 5 Programmatic Management of Drug-resistant TB (PMDT) treatment sites: 18 District/subdistrict level: 18
PAPUA NEW GUINEA	21 devices in total; all are 4-module devices	Reference laboratory and district level hospital
RUSSIAN FEDRATION	73 devices implemented in the country (in the public sector). No data about number of modules.	Not known
SOUTH AFRICA	1294 devices in 207 sites (as of 2014)	Not known
SWAZILAND	38 devices in total as of Sept 2015; all are 4-module devices, except 1 16-module device in the Mbabane Government Hospital Laboratory	District Hospitals: 9 Health Centres (subdistrict): 5 Clinics: 3 NGOs: 6 Private: 5 Some of the facilities have 2 units of 4 modules
TAJIKISTAN	15 devices in total; 1 2-module device at the National Reference Laboratory and the rest (14) are 4-module devices	National reference laboratory: 1 National TB center microscopy laboratory: 2 Regional TB centers: 3 Paediatric TB hospital: 1 District level microscopy center level: 8
UKRAINE	30 devices in total; includes 28 4-module devices and 1 2-module device; In addition to this, GFATM purchased 10 more 4-module devices; In the prison sector: 8 4-module devices; 10 4-module devices; All devices procured under the GFATM are in the process of being installed;	National Reference Laboratory: 1 3rd Level lab: 29 (28 4-module devices and 1 1-module device 3rd level prison labs: 8 (a 4-module device in each lab) 2nd level labs: 3 (2 4-module devices and 1 1-module device 1st lab level (AIDS centre): 7 (a 4-module device in each lab) In the process of installing 3 4-module devices.
UZBEKISTAN	25 devices in total Karakalpakstan: 6 (plus 2 in the pipeline) Rest of Uzbekistan: 19	Karakalpakstan: Central level: 5; District level: 1 By the end of 2015: Central level: 5; District level: 3 Tashkent: National AIDS centres: 2 National Reference Laboratory: 2 Oblast (state level) and Rayon level: 15
VIET NAM	32 devices in total, of which 30 are for public use as per the National Strategic Plan drafted in mid-2014. However, a total of 46 GeneXpert devices are mentioned as recently as December 2014 (according to the 20.20130419 WHO PMDT Monitoring Mission Report, page 22: In 2012, 7 sites; in 2013, 17 sites; and 2014-2015, 43 sites. A total of 43 GeneXpert machines are to be installed between 2013 and 2015).	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/subdistrict level: 6 (3 in each district treatment unit in Hanoi and Ho Chi Minh City)Microscopy centre level: 0 (likely included above) Community outreach or mobile clinics: 0 (Page 22, 20.20130419 WHO PMDT Monitoring Mission report)
ZIMBABWE	96 devices in total, including 93 4-module devices and 3 16-module devices	Reference laboratory: 2 Specialized hospitals: 3 Provincial Hospitals (including 2 major city hospitals): 10 District/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, lead analyst and writer; Greg Paton, project manager and writer, and Sahu Suvanand, technical expert.

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