OUT OF STEP 2017

TB Policies in 29 Countries

A survey of prevention, testing and treatment policies and practices

MEDECINS SANS FRONTIERES

Stop TB Partnership

Médecins Sans Frontières (MSF)

MSF is an independent international medical humanitarian organisation that delivers medical care to people affected by armed conflicts, epidemics, natural disasters and exclusion from health care. 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. MSF has TB treatment projects in 24 countries; it is one of the largest non-governmental providers of treatment for drug-resistant TB. In 2016, MSF supported more than 20,000 TB patients on treatment, including 2,700 patients with drug-resistant forms of TB.

Largely in response to the inequalities surrounding access to HIV/AIDS treatment between rich and poor countries, MSF launched the Access Campaign in 1999. 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.

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 and diagnostics to countries around the world, and TB REACH, which has helped diagnose and treat over 2 million people with TB by providing small grants to identify and scale up innovative approaches to TB.

The Stop TB Partnership and its 1,600 partners are a collective force that is transforming the fight against TB in more than 110 countries. They include international and technical organisations, government programmes, research and funding agencies, foundations, NGOs, civil society and community groups, and the private sector.

The 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.

Out of Step is dedicated to people affected by TB around the world who are fighting for the treatment they need, many of whom are still unable to access the latest diagnostics and medicines. No one should die of a curable disease for reasons of geography or economic status.

Out of Step 2017
TB policies in 29 countries

A survey of prevention, testing and treatment policies and practices
July 2017

To access the report online:
MSF: msfaccess.org/outofstep2017
Stop TB: stoptb.org/outofstep
#StepUpforTB Campaign: stepupfortb.org

Front cover photo: Sven Torfinn

OUT OF STEP 2017

TB Policies in 29 Countries

A survey of prevention, testing and treatment policies and practices

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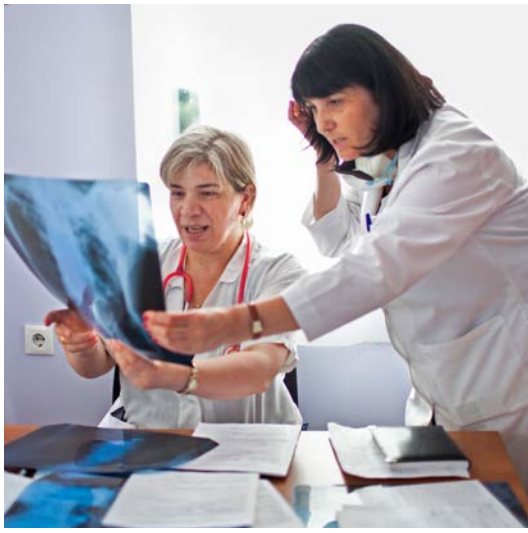

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A YOUNG GIRL SITS ON THE WINDOW OF HER HOUSE IN ANATARIPARA RASWAMORI IN KOTRI, PAKISTAN.

EXECUTIVE SUMMARY

Although it can be prevented and successfully treated, tuberculosis (TB) is the world's deadliest infectious disease: in 2015, 1.8 million people died from it.[1] While there have been substantial and important innovations in the fight against TB, including faster, more accurate diagnostic tests and the first new medicines in nearly 50 years, deadly gaps remain in implementing and providing access to these advances. Outdated policies, practices and tools for diagnosing, as well as conservatism and inaction in registering and using new TB medicines, are key barriers to turning around the TB epidemic.

Adopting and implementing internationally recognised TB policies and guidelines from the World Health Organization (WHO) is fundamental to ending TB by 2030. But the *Out of Step 2017* report reveals that many countries still lag behind in ensuring full implementation of the WHO guidelines and policies that are proven to reduce TB incidence and death.

Out of Step includes the results of a 29-country survey on national TB policies and practices. The report was created to identify gaps in implementation and monitor progress towards ending TB.

While countries have made progress since the 2015 *Out of Step* report, much more work needs to be done to make sure that these policies are fully implemented across all communities, so that they will make a real difference to people affected by TB.

COUNTDOWN TO 2030

In 2015, world leaders endorsed the United Nations Sustainable Development Goals, which include an ambitious but achievable target to end the TB epidemic by 2030.[2] The WHO's End TB Strategy, which was approved by the World Health Assembly in 2014, calls for bold policies and supportive systems at the national level, and reductions in TB incidence (by 80% from 2015) and TB deaths (by 90% from 2015) by 2030.[2]

The Stop TB Partnership's Global Plan to End TB 2016-2020 sets out the actions and resources needed by 2020 if the world is to end the epidemic by 2030[3]; it challenges countries to reach the 90-(90)-90 targets: to have 90% of all people with TB diagnosed and successfully treated, including 90% of vulnerable populations.

Diagnosing TB quickly and accurately, so that people receive appropriate treatment, is an imperative first step. While many countries have adopted WHO guidelines and policies for diagnosis, the glacial pace of implementation is costing both lives and livelihoods. In 2015, more than 4 million people with TB went undiagnosed, and less than 25% of people estimated to have drug-resistant TB were diagnosed and treated.[1]

The first step to closing the deadly diagnostic gap is initial testing for all with Xpert MTB/RIF, a rapid molecular test that can diagnose TB and detect rifampicin resistance in 2 hours. For people with rifampicin-resistant (RR) TB, additional drug-sensitivity testing (DST) should be available so that they can be treated with medicines most likely to be effective. In the 29 countries surveyed, 52% (15) have adopted a policy of 'Xpert for all' and 47% (7/15) of them have widely implemented the test. Of all countries that provide initial testing with Xpert MTB/RIF only to high-risk groups (people living with HIV and people at risk for drug-resistant forms of TB), only 54% (15/28) have widely implemented it. Universal DST must be scaled up: 62% (18) of countries recommend it and 50% (9/18) of those have widely implemented it.

With such a low proportion of countries having fully implemented recommended tests, the diagnostic gap remains massive; this deadly gap must be closed so that countries can reduce TB illness and death.

Once a person with TB has been properly diagnosed and started on treatment, ongoing care must be patient-centred, and easily accessible to all who need it. It has been more than 50 years since WHO recognised that limited resources were best used for ambulatory TB care, instead of hospital beds. Decentralising TB treatment relieves the deadly bottleneck delaying treatment initiation, lowers the cost of treating TB and is preferred by patients. Community health workers can improve drug-resistant (DR) TB treatment adherence by providing education, support and counselling and they facilitate decentralisation of DR-TB treatment.

Drug-sensitive (DS) TB treatment is started at the primary health care level in 83% (24) of countries (in some countries exceptions are made for people who are smear-negative and on a case by case basis), and 83% (20/24) of them have implemented the policy widely. Only 52% (15) of countries allow nurses and other health care workers to start adults on treatment for DS-TB. In 66% (19) of countries surveyed, treatment for DR-TB is initiated at the district level; but only 58% (11/19) of them have implemented the policy widely. Although hospitalisation should be reserved only for the sickest DR-TB patients, 34% (10) of countries still require it for nearly all patients. These results indicate that the

decentralisation of patient-centred care must significantly accelerate if countries are to seriously improve treatment outcomes for people diagnosed with TB.

TB is the leading cause of death among HIV-positive people; HIV increases vulnerability to TB by up to 31-fold.[4] In 2015, 400,000 HIV-positive people died of TB.[1] Antiretroviral therapy (ART) lowers the risk for TB, and is recommended by WHO for all HIV-positive people[5]. Yet, only 38% (11) of countries have adopted 'HIV test-and-start' policies, and only 73% (8/11) of them have implemented the policy widely. These findings illustrate that much more needs to be done to prevent people living with HIV from developing and dying from TB co-infection.

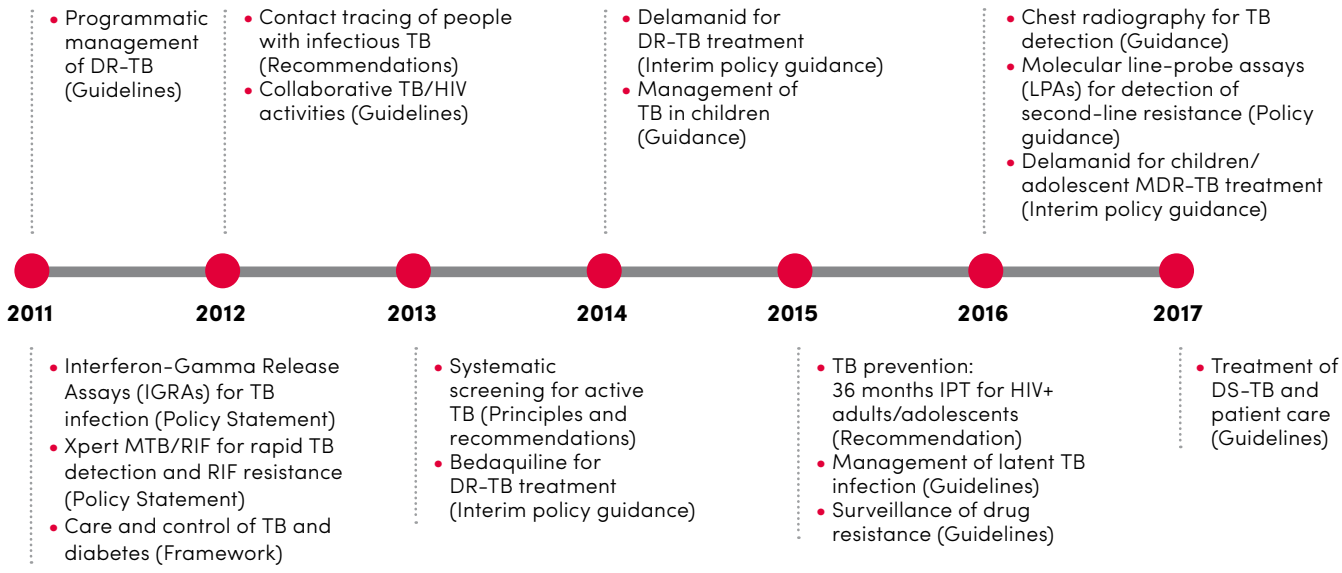
Children are especially vulnerable to TB. In 2015, 1 million children fell ill with TB[1], and approximately 169,000 children aged 0-14 died from it.[1] The lack of child-friendly drug formulations has complicated paediatric TB treatment, but child- and caregiver-friendly paediatric fixed-dose combinations (FDCs) for DS-TB are now available and recommended by WHO. In 50% (14/28) of countries, the new paediatric FDCs for DS-TB are the standard of care, but only 29% (4/14) of them have widely implemented this policy. Children have long been neglected in TB care due to the difficulty of diagnosing and treating the disease. Nevertheless, governments must clearly do more to ensure the new paediatric formulations are reaching patients.

Treatment for DR-TB can be shortened to 9 months in certain circumstances; for people who are eligible, shorter treatment is equally effective and spares them from months of terrible side effects, and saves money. But only 45% (13) of countries recommend it, and only 69% (9/13) of them have implemented it, but not widely. Bedaquiline and delamanid, newer TB medicines recommended for people with few or no TB treatment options, are included in 79% (23) and 62% (18) of national guidelines, respectively. Globally, however, only about 5% of people with DR-TB have access to these life-saving medicines. *Out of Step* reveals that countries are too conservative in implementing new treatment regimens that could significantly improve cure rates for DR-TB, and help curb the spread of drug-resistant strains.

Access to new treatments must be accelerated. This requires that governments take bold steps in how drugs are regulated and made available in their countries. Only 75% (21/28) of countries have accelerated registration mechanisms in place, while 89% (25/28) of countries allow access to unregistered TB medicines through compassionate use programmes, import waivers, or by other means. Furthermore, 41% (12) are enrolled in the WHO Collaborative Registration Procedure, which accelerates approval of and access to originator and generic medicines, including TB medicines, for public health needs in developing countries. None of the 29 countries surveyed list all of the anti-TB medicines recommended by WHO for the treatment of DR-TB in their national Essential Medicines List (EML) in the TB medicines section and only 25% (7/28) include bedaquiline or delamanid in their national EML.

TB can be prevented. Preventive therapy can stop people with latent TB infection (LTBI) from developing active TB disease. But access is not universal; while all of the countries provide it to the most vulnerable groups (child contacts and HIV-positive people), 31% (9) of these countries have not implemented it widely. Only 14% (4) of countries provide preventive therapy to other high-risk

TIMELINE OF KEY WHO POLICIES AND GUIDELINES (2011–2017)



groups, and only 14% (4) of countries also provide it to adult contacts. Countries must pay more attention to TB prevention if they are to make serious inroads in stopping the spread of this debilitating and deadly disease.

The *Out of Step* findings clearly show that governments must re-commit to fighting and winning the battle against TB, with urgency.

Global health actors, governments and donors urgently need to step up to stop the world's poorest and most vulnerable people from needlessly falling ill, suffering and dying from TB. Although we have modern tools for fighting this ancient disease, we aren't using them enough - especially in the places where they are needed the most. We are still out of step in preventing and diagnosing TB, providing patient-centred care, and accelerating research into, registration and delivery of new, life-saving medicines.

We urgently need political will and adequate resources to fight TB; only a third of the annual funding needed to meet the 2030 targets is being provided. Without funding, we will not be able to fully roll out the policies, practices and tools that spare people with TB from avoidable suffering and death.

STEPPING UP: Progress in adopting TB policies (2015–2017)*

A comparison of select policies for countries that were surveyed in the *Out of Step* 2015 and 2017 reports

Diagnosis

In 2015, only 32% of countries (7/22) had a policy in place for using Xpert MTB/RIF as the initial diagnostic test for all. By 2017, this percentage doubled to 68% (15/22) of countries. Xpert MTB/RIF was already widely available in 2015 as the initial diagnostic test for high-risk groups and, since then, some progress has been made towards Xpert MTB/RIF for all. But Xpert MTB/RIF was recommended in 2010; 7 years later, only 15/29 countries are using it as the initial test for TB. Although Xpert MTB/RIF should replace sputum smear microscopy since it is faster and more accurate, microscopy remains the mainstay of TB diagnosis in many countries.

Models of care

The number of countries where DS-TB treatment can be initiated at the primary health care level has increased from 73% (16/22) in 2015 to 82% (18/22) in 2017. Decentralising DR-TB services is more complex, since people with DR-TB may be sicker and suffer from side effects of their treatment. Nonetheless, the number of countries where DR-TB treatment can be initiated at the district level increased from 62% (13/21) in 2015 to 67% (14/21) in 2017.

The number of countries requiring routine hospitalisation for most DS-TB patients decreased slightly from 23% (5/22) in 2015 to 18% (4/22) in 2017. The trend is similar for DR-TB patients; routine hospitalisation decreased from 40% (8/20) in 2015 to 25% (5/20) in 2017. Hospitalisation should not be routinely recommended - or made compulsory - for people undergoing TB treatment, unless it is medically necessary (if they are very ill or have severe side effects that need monitoring and management).

Bedaquiline and delamanid

In 2015, bedaquiline was included in national guidelines in 48% (10/21) of countries and delamanid was included in national guidelines in only 14% (3/21). In 2017, bedaquiline has been included in national guidelines in 86% (18/21) of countries, and delamanid has been included in guidelines in 67% (14/21). People who have no other treatment options for their DR-TB need access to these life-saving medicines, so access to them needs to increase.

Regulatory environment for TB medicines

In 2015, 65% (15/23) of countries had legal mechanisms to allow access to unregistered medicines. In 2017, this increased to 91% (21/23) of countries. Medicine registration can often take years, depending on both the willingness of the manufacturer and the country's regulatory capacity; so mechanisms that allow access to unregistered new and repurposed TB medicines for people who need them are important.

In 2015, 56% (13/23) of countries had mechanisms in place to allow for accelerated registration of medicines (potentially for DR-TB medicines). In 2017, the number of countries with these mechanisms increased to 78% (18/23). Since registration might take up to 2 years in some countries, accelerated mechanisms for key DR-TB medicines are important so that they become available as soon as possible.

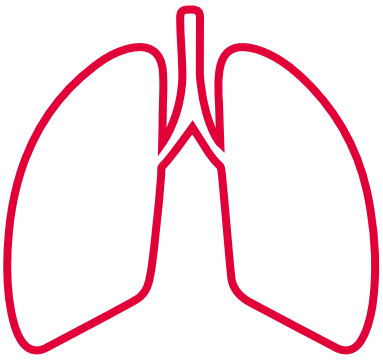
In 2015, 76% (16/21) of countries required a prescription for TB medicines; in 2017, this figure increased to 95% (20/21) of countries. This requirement could prevent the rise and spread of drug-resistant forms of TB.

* Data were considered where the information was available and answers could be verified.

PERCENTAGE OF PEOPLE WITH TB DIAGNOSED AND NOTIFIED TO WHO IN OUT OF STEP COUNTRIES (2015) *

<25%
Nigeria

25–49%
Dem. Rep. of Congo
Indonesia
Mozambique



50–74%
Afghanistan
Bangladesh
Belarus
Cambodia
Central African Rep.
Ethiopia
India
Myanmar
Pakistan
South Africa
Swaziland
Ukraine
Zimbabwe

75–90%
Armenia
Brazil
China
Georgia
Kazakhstan
Kenya
Kyrgyzstan
Philippines
Papua New Guinea
Russian Federation
Tajikistan
Viet Nam

#STEPUPFORTB CAMPAIGN

Every 18 seconds a person dies from TB, but this can change if governments implement the current policies and practices recommended by WHO. The #StepUpforTB campaign, a collaboration between MSF and the Stop TB Partnership, aims to increase awareness about how the gaps in TB policies and practices lead to unnecessary TB deaths around the world. The goal of the #StepUpforTB campaign is to encourage governments to adopt and implement up-to-date TB policies and guidelines by World TB Day 2018. #StepUpforTB is a communication platform that uses social media posts and petitions; it also provides personal stories from TB survivors and activists, along with evidence supporting the best policies and practices. These resources will inform and empower campaigners to push governments towards closing the deadly TB diagnosis and treatment gaps.

Join the #StepUpforTB campaign at:
http://stepupfortb.org/

*Diagnosed and notified to WHO for 2015. The case detection rate was calculated as the number of cases notified divided by the number of cases estimated for that year, expressed as a percentage.

METHODOLOGY

Out of Step reports

The *Out of Step* reports were created to identify gaps and monitor progress in adoption of international standards into national TB policies and practices. Countries can use *Out of Step* to measure or compare their progress, and TB advocates can use it to inform their efforts. The first edition, published in 2014, monitored progress in eight countries, including those with a high burden of TB. The second edition, published in 2015, covered 24 countries.

The 2017 edition of *Out of Step* covers five key areas: diagnostics, models of care, treatment for drug-sensitive (DS) and drug-resistant (DR) TB, drug regulation, and prevention. *Out of Step 2017* includes 23 of the 24 countries from the 2015 edition plus six additional countries where there is a Stop TB Partner or MSF project and the country has a high burden of TB and/or TB/HIV and/or multidrug-resistant (MDR)-TB according to WHO criteria.[1] All but three countries (Afghanistan, Armenia and Georgia) are included in at least one of these high-burden categories, as defined by WHO.[1]

The 29 countries surveyed for this edition of *Out of Step* are home to 82% of the global TB burden.[1] These are: Armenia, Afghanistan, Bangladesh, Belarus, Brazil, Cambodia, Central African Republic (CAR), China, Democratic Republic of Congo (DRC), Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Myanmar, Nigeria, Pakistan, Papua New Guinea (PNG), Philippines, Russian Federation, South Africa, Swaziland, Tajikistan, Viet Nam, Ukraine and Zimbabwe.

Development and content of the questionnaire

> MSF and Stop TB Partnership developed a semi-structured questionnaire to assess the national adoption and implementation of TB diagnostics, models of care, treatment for DS- and DR-TB, the regulatory environment for TB medicines, and TB prevention. The questionnaire was developed between September and November 2016 by experts from MSF and Stop TB Partnership.

Process for data collection, analysis and validation

From October to mid-November 2016, MSF and Stop TB Partnership conducted a desktop review of current TB and HIV policy documents and guidelines from each country. In November 2016, each national TB programme (NTP) manager received a list of country-level documents and a request for additional information (national Ministry of Health [MoH]-approved policy documents and guidelines covering the five key areas of *Out of Step*), as needed. They were given 3 weeks to review the information that was provided and share updates about the status of their national policies and guidelines, including whether the policies and guidelines were in the process of being updated or if new versions had been drafted. Of the 29 NTPs, 21 responded and approved the existing documents or provided additional documents. Countries that did not share their guidelines were sent requests and reminders via email and phone calls.

MSF followed up in the 18 countries where it has TB projects (Armenia, Belarus, Brazil, CAR, DRC, Georgia, India, Kenya, Kyrgyzstan, Mozambique, Myanmar, PNG, Russian Federation, South Africa, Swaziland, Tajikistan, Ukraine and Zimbabwe), and Stop TB Partnership followed up in the remaining countries (Afghanistan, Bangladesh, Cambodia, China, Ethiopia, Indonesia, Kazakhstan, Nigeria, Pakistan, Philippines and Viet Nam). In some cases, MSF and Stop TB Partnership worked together to collect data from NTPs.

Stop TB Partnership used the information from the NTPs and the desktop review to pre-fill the questionnaires for 11 countries. These were sent to the NTPs to ensure that the answers reflected the national TB policies and guidelines, and that the level of implementation for each was accurately characterised. If there were discrepancies in the answers, clarification or additional documents were sought from respondents. In some cases, the questionnaire was shared multiple times until any doubts or concerns about the questions were resolved. Once completed, each questionnaire was reviewed by an independent, professional fact checker and TB experts from MSF and Stop TB Partnership. This validation process began in February 2017 and was completed in mid-May 2017.

Phone calls to collect and validate information were made between February and May 2017. Stop TB Partnership and MSF country teams exchanged numerous phone calls and emails with NTPs.

MSF shared the questionnaire with country teams on 1 December 2016 for completion by 20 January 2017. In eight countries, MSF teams worked closely with the NTPs

to complete the questionnaire. If the NTP did not share any documents, MSF country teams obtained national documents to fact-check the NTP's responses. The full list of references is included in the online version of the report, available at: stepupfortb.org. After MSF teams completed the questionnaires, they were checked by a Stop TB staff member. The questionnaires were then returned to the MSF country teams to clarify responses over multiple rounds of phone calls. Once questions were resolved, each questionnaire was reviewed by a fact checker and a team of MSF pharmacists and diagnostic and treatment experts. The validation process was completed in the third week of May 2017.

Challenges

For the eight countries where there was no response from NTPs, MSF country teams provided the necessary documents to complete the survey. Source documents were often available only in the local language; these were translated from Russian, Portuguese and Armenian by a professional, UN-approved translation services company.

The questionnaire consisted of two main parts. The first part asked whether national policies were aligned with current WHO guidelines, calling for yes or no answers; in cases where there was no response, the answer was recorded as 'unknown'. The second part included questions about the implementation of policies, asking whether and how widely they had been implemented. One limitation of the data on implementation was that there were only three possible responses ('yes', 'yes, but not widely', or 'no'). In some cases, the level of implementation may have been over-reported, as 'yes but not widely' may have been interpreted differently by each country. If the answer about an existing policy was 'no', responses about implementation were not included in this report.

In a few cases, there was confusion over the responses*. In such instances, we tried to clarify these responses with the NTPs and country teams via phone and email exchanges. If responses could not be clarified, the answer was considered to be 'unknown'. In countries where MSF does not have TB operations, Stop TB Partnership contacted the NTPs to validate information. There was no response to our numerous phone and email attempts from the NTP of Indonesia, hence the questionnaire for Indonesia could not be validated.

If information was not provided by countries and could not be found by reviewing source documents and country guidelines, the response was recorded as 'unknown'.

Data were collected until mid-May 2017.** Since there is a lag between the release of WHO guidelines and their adoption by countries, some countries were in the process of updating their guidelines during the survey period. If guidelines were being updated at the time of the survey and the NTP or country office provided information about their content, the status of the document was noted.

Interpretation of answers/results

Key findings are provided for each area, reported as both percentages and numbers. Unless noted, the denominator is 29, for all countries included in the survey. If a country did not answer a question, both the numerator and denominator were adjusted.

*One question in the survey asked countries if chest x-ray should be carried out to identify people who need to be tested with Xpert MTB/RIF. Most respondents did not understand the question; the majority actually answered 'Yes' if chest x-ray was a part of the overall diagnostic package, regardless of whether or not chest x-ray was used as a screening tool to identify Xpert-eligible patients. For this reason, it was not possible to interpret national x-ray policies.

**Questions about policies and implementation of TB-LAMP (loop-mediated isothermal amplification; a test that WHO recommends to replace microscopy for diagnosing pulmonary TB in adults with signs and symptoms of TB) were not included in the survey, since the guidance was very new when the data collection began.

A WOMAN WITH MDR-TB WITH HER SON WHO IS ALSO BEING TREATED FOR MDR-TB IN UKRAINE.

KEY POLICIES DASHBOARD

COUNTRY	DIAGNOSIS				MODELS OF CARE				
	Xpert MTB/RIF is the initial TB diagnostic test for adults and children being investigated for TB	TB-LAM is used to diagnose TB in PLWHA with CD4 ≤ 100 µL or seriously ill	First-line DST (rifampicin and isoniazid) is done for all RR-TB cases or for people at risk of DR-TB	Second-line DST (fluoroquinolones & second-line injectable agents) is done for all DR-TB cases	DS-TB treatment is started at the primary health care level*	DR-TB treatment is started at the district level*	Hospitalisation is NOT required for DS-TB treatment *,◆	Hospitalisation is NOT required for DR-TB treatment *,◆	ARV treatment is offered to all PLWHA ('test and start')
Afghanistan	●	●	●	●	●	●	●	●	●
Armenia	● [a]	●	●	●	● [h]	● [h]	●	● [h]	●
Bangladesh	●	●	●	●	●	○	●	●	●
Belarus	● [b]	●	●	●	●	●	● [h]	● [h]	●
Brazil	●	●	●	●	●	●	●	●	●
Cambodia	●	●	●	● [c]	●	●	●	●	⊗
CAR	●	⊗	○	?	●	●	●	●	●
China	●	●	●	●	●	●	●	●	●
DRC	●	●	●	● [c]	●	●	●	●	●
Ethiopia	●	●	●	○	●	●	●	●	●
Georgia	●	●	●	●	● [i]	● [h]	●	●	●
India	●	●	○	○	●	●	●	●	●
Indonesia	○	●	?	○	?	?	●	●	●
Kazakhstan	●	●	●	●	●	●	●	●	●
Kenya	○	●	●	○	●	●	●	●	●
Kyrgyzstan	○ [d]	●	○	○	○	●	●	●	●
Mozambique	○	●	○	● [e]	●	○	●	●	○
Myanmar	●	●	○ [f]	● [f]	●	○	●	●	●
Nigeria	○	●	●	⊗	●	●	●	●	●
Pakistan	●	●	●	?	?	●	●	●	●
PNG	○	●	○	○	●	●	●	●	●
Philippines	●	●	○	○	●	○	●	●	●
Russian Fed.	○ [g]	●	●	○	●	● [j]	●	●	●
South Africa	●	●	●	●	●	?	●	●	○
Swaziland	●	●	●	●	●	●	●	●	●
Tajikistan	○	●	○	○	○	○	●	●	●
Ukraine	●	●	●	●	●	⊗	●	●	●
Viet Nam	●	●	●	●	●	●	●	●	● [k]
Zimbabwe	●	⊗	●	●	●	●	●	●	●

(*) Including smear-positive individuals. In some countries exceptions are made for people who are smear-negative and on a case by case basis. **(◆)** The implementation of the policy was not assessed for the hospitalisation questions. **(***)** Compassionate use, expanded access programmes, import waivers or other legal mechanisms. **(a)**The initial diagnostic test is microscopy but regardless of microscopy result, every person to be evaluated for TB is tested with Xpert. **(b)** Part of an initial diagnostic package of tests. **(c)** Only select groups of patients are eligible. **(d)** At facilities that offer DR-TB regimens with BDQ or DLM. **(e)** No, but second-line DST is available at National Reference Lab. **(f)** Implementation of the 2017 guidelines is expected for the second half of 2017. **(g)** Xpert is part of a package of diagnostic tools; other diagnostic tests can be used, including other rapid molecular methods. **(h)** Except for people who are smear-negative and on a case by case basis. **(i)** Patient receives a prescription at TB facilities. **(j)** DR-TB treatment can be started and dispensed from

COUNTRY	TB AND DR-TB TREATMENT				MEDICINES REGULATORY ENVIRONMENT		
	New paediatric TB FDCs are the standard of care	National policy reflects WHO guidance on bedaquiline use for adults	National policy reflects WHO guidance on delamanid use for adults and children	National policy includes the WHO-recommended, 9-month (shorter) MDR-TB treatment regimen	DR-TB medicines can receive accelerated registration	Unregistered TB medicines are available through CU/other legal mechanisms***	Country is enrolled in WHO Collaborative Registration Procedure
Afghanistan	?	✗	✗	?	●	●	●
Armenia	●	●	●	●	●	●	●
Bangladesh	?	?	?	○	● [p]	●	●
Belarus	●	●	●	●	●	●	●
Brazil	●	●	●	●	●	●	●
Cambodia	?	?	?	?	●	●	●
CAR	○	●	●	○	●	●	●
China	●	●	●	●	●	●	●
DRC	●	○	●	○	●	●	●
Ethiopia	✗	●	●	● [m]	●	●	●
Georgia	●	●	✗	●	● [q]	●	●
India	✗	○	●	●	●	●	●
Indonesia	●	?	●	●	●	●	●
Kazakhstan	●	?	?	●	?	?	●
Kenya	○	○	○	●	●	●	●
Kyrgyzstan	?	○	✗	○	●	●	●
Mozambique	?	○	○	● [n]	●	●	●
Myanmar	✗	●	●	○	●	●	●
Nigeria	●	●	○	●	●	●	●
Pakistan	● *	?	?	●	●	●	●
PNG	○	○	○	○	●	●	●
Philippines	●	○	○	?	●	●	●
Russian Fed.	●	●	●	●	●	●	●
South Africa	●	○	○	● [o]	●	●	●
Swaziland	●	●	●	○	● [r]	●	●
Tajikistan	●	● [l]	● [l]	○	●	●	●
Ukraine	●	●	●	●	●	●	●
Viet Nam	●	●	●	○	●	●	●
Zimbabwe	●	○	○	✗	●	●	●

LEGEND

Is this policy in place at the national level? ● Yes ● No (?) Unknown

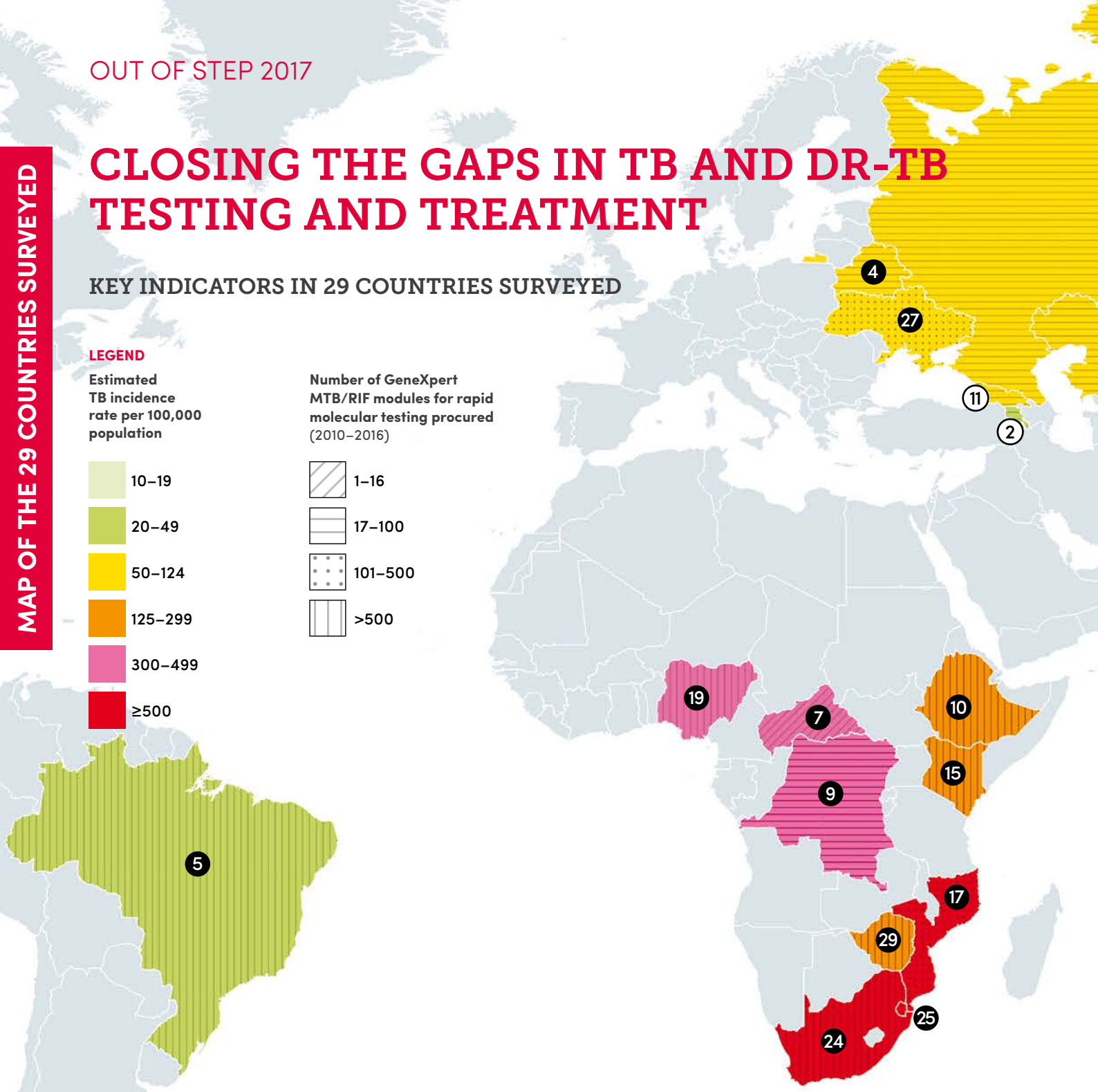
If Yes, is the policy being implemented? ● Yes ○ Yes, but not widely ✗ No (?) Unknown

the district level, but only after decision and prescription from the regional TB committee. **(k)** Test and start in mountainous, coastal and remote provinces. **(l)** Implementation in pilot sites. **(m)** Will be included in the new paediatric guidelines. **(n)** New DR-TB guidelines in development include shorter MDR-TB regimens per WHO criteria and the NTP plans to enroll the first patients in July 2017. **(o)** New DR-TB guidelines in development include shorter MDR-TB regimens. **(p)** Only upon government declaring an emergency. **(q)** Only if already approved by an SDRA. **(r)** There is currently no regulatory medical authority in Swaziland.

MAP OF THE 29 COUNTRIES SURVEYED

CLOSING THE GAPS IN TB AND DR-TB TESTING AND TREATMENT

KEY INDICATORS IN 29 COUNTRIES SURVEYED



MDR-TB TREATMENT COVERAGE
(percentage of people who started MDR-TB treatment relative to estimated incidence of MDR-TB)

TB/HIV CO-INFECTION RATE
(percentage of people with TB who are estimated to be HIV-positive)

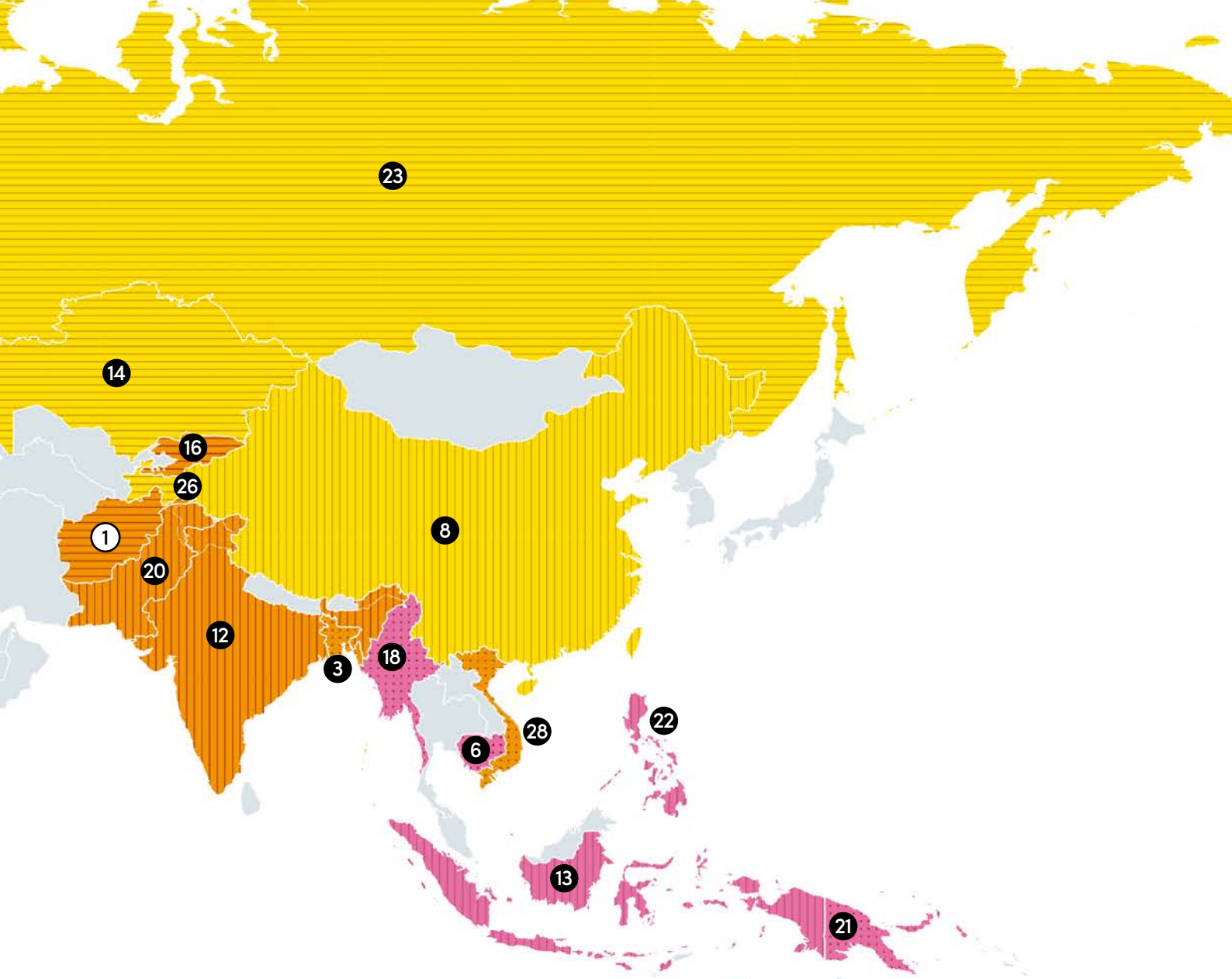
GAP BETWEEN ESTIMATED AND DETECTED CASES
(percentage of people estimated to have TB that are missing in the country's case detection rates)

WHO HIGH TB OR HIGH TB/HIV OR HIGH MDR-TB BURDEN COUNTRIES

OTHER

SOURCES: All information is from 2015 except where noted.
WHO: http://www.who.int/tb/country/data/download/en (Accessed 2017 May 31)
Data on procurement of GeneXpert MTB/RIF modules were obtained from its manufacturer Cepheid

DISCLAIMER: Boundaries used on this map do not imply the expression of any opinion whatsoever on the part of the Stop TB Partnership concerning the legal status of any country or territory or of its authorities, or concerning the delimitation of its frontiers or boundaries



1 Afghanistan — 3% | 1% | 42%

2 Armenia — 37% | 9% | 11%

3 Bangladesh — 9% | 0% | 43%

4 Belarus — 54% | 6% | 28%

5 Brazil — 27% | 15% | 13%

6 Cambodia — 6% | 2% | 41%

7 Central African Republic — 18% | 45% | 45%

8 China — 8% | 2% | 13%

9 Democratic Republic of the Congo — 4% | 15% | 52%

10 Ethiopia — 10% | 8% | 29%

11 Georgia — 42% | 6% | 20%

12 India — 21% | 4% | 41%

13 Indonesia — 5% | 8% | 68%

14 Kazakhstan — 74% | 3% | 11%

15 Kenya — 18% | 33% | 24%

16 Kyrgyzstan — 23% | 3% | 18%

17 Mozambique — 9% | 52% | 62%

18 Myanmar — 16% | 9% | 30%

19 Nigeria — 2% | 17% | 85%

20 Pakistan — 10% | 2% | 37%

21 Papua New Guinea — ?% | 15% | 20%

22 Philippines — 24% | 1% | 15%

23 Russian Federation — 37% | 10% | 13%

24 South Africa — 62% | 57% | 37%

25 Swaziland — 34% | 72% | 41%

26 Tajikistan — 33% | 3% | 20%

27 Ukraine — 38% | 22% | 26%

28 Viet Nam — 29% | 4% | 21%

29 Zimbabwe — 24% | 69% | 28%

AN MSF STAFF MEMBER USING A GENEXPERT MACHINE IN PRIMEIRO DE MAIO HEALTH CENTRE, MOZAMBIQUE.

DIAGNOSIS

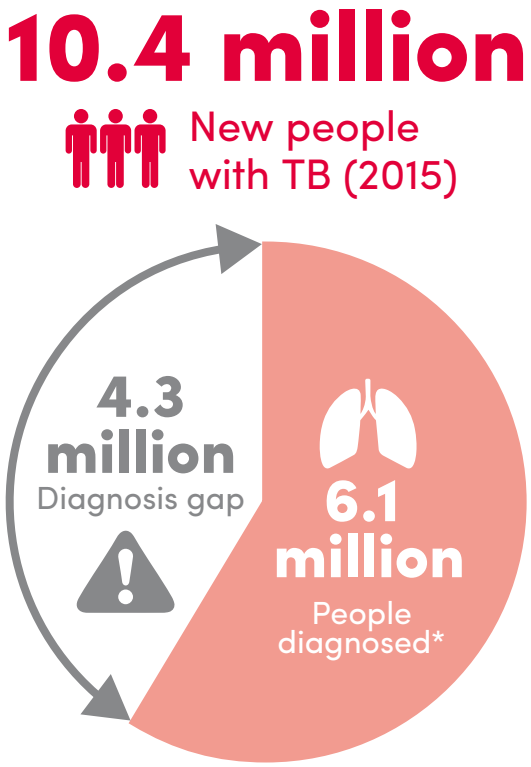
KEY FINDINGS

- Xpert MTB/RIF is recommended as the initial test for all by 52% (15) of countries;
- Nationwide implementation of Xpert MTB/RIF as the initial test for TB lags behind, as only 47% (7/15) of countries have made Xpert MTB/RIF widely accessible;
- More countries recommend Xpert MTB/RIF as the initial test for all in 2017 than in 2015: 68% (15/22)* versus 32% (7/22)*;
- Xpert MTB/RIF is used as the initial diagnostic test only for high-risk groups (people living with HIV and people at risk for DR-TB) in 97% (28) of countries, but only 54% (15/28) of them have implemented it widely;
- Rifampicin resistance testing for all people with bacteriologically confirmed TB was recommended in the guidelines in 72% (21) of countries;
- Second-line drug-sensitivity testing (DST; at least for second-line injectable drugs [SLIDs] and fluoroquinolones [FLQs]) for all rifampicin-resistant (RR) and MDR-TB cases is recommended in guidelines in 83% (24) of countries;
- Universal DST (DST for rifampicin resistance [RIF-DST] for all people with bacteriologically confirmed TB followed by second-line DST for FLQs and SLIDs for all people with RR-/MDR-TB) is recommended in the guidelines in 62% (18) of countries;
- Universal DST has been widely implemented in 50% (9/18) of these countries;
- Only two countries, CAR and Zimbabwe, include TB lipoarabinomannan (TB-LAM) in their guidelines, although it has not been implemented;
- 56% (15/27) of countries have guidelines that require line probe assays (LPAs) for second-line drug-resistance testing (to FLQs and SLIDs) as the initial test for people with confirmed RR- and MDR-TB.

BACKGROUND

The first step towards reducing sickness and the spread of TB is diagnosing it quickly and accurately, so that people can receive appropriate treatment. Yet, millions of people with TB have died, many before they were diagnosed, without the chance to be cured. In 2015, over 4 million people with TB went undiagnosed, and less than 25% of people estimated to have DR-TB were diagnosed and treated.[1]

* Data were considered where the information was available and answers could be verified.



* 6.1 million new TB cases were notified to national authorities and reported to WHO in 2015.

To close the diagnostic gap, the End TB Strategy calls for all countries to implement initial diagnostic testing with a WHO-recommended rapid diagnostic test that can also detect resistance to rifampicin by 2020, and by 2018 in countries with high burdens of TB, MDR-TB and TB/HIV co-infection.[6] By 2025, ≥90% of people should be diagnosed with a WHO-recommended rapid test, and 100% of those diagnosed should receive DST.[6]

Xpert MTB/RIF (and the next-generation version, Xpert MTB/RIF Ultra)[7] are WHO-recommended rapid diagnostic tests that can diagnose TB and detect rifampicin resistance in 2 hours.[8] Xpert MTB/RIF is more accurate and faster than conventional diagnostics, such as sputum smear microscopy and culture.[6]

Yet many countries still do not use Xpert MTB/RIF as the initial test for all. In 2015, *Out of Step* reported that only 7 of 24 countries were using Xpert MTB/RIF as the initial diagnostic test for all.[9] For this report, we found that 52% (15) of countries have guidelines that recommend using rapid molecular tests as the initial diagnostic, but only 47% (7/15) of them are widely implementing this policy.

Although Xpert MTB/RIF has many advantages, there are financial, logistical and operational challenges associated with its implementation and scale-up. In many countries, TB REACH-supported projects have provided lessons learned and experience for early adopters.[10] In some places, MSF has observed that

the machines have arrived just to sit in storerooms unplugged because there is no stable power supply or insufficient resources for cartridges.

TB is harder to diagnose in people living with HIV, since some of them have extrapulmonary TB or are too sick to produce sputum samples. A novel diagnostic with the potential to overcome these challenges is TB-LAM, a urine-based, rapid point-of-care test. WHO recommends TB-LAM specifically – and only – for helping to diagnose TB in people living with HIV with CD4 cell counts of ≤100 cells/μL and TB symptoms, or for any HIV-positive person who is very ill.[11]

TB drug-resistance testing and effective treatment are essential to halting illness and death from, and the onward transmission of, DR-TB. Although rapid molecular tests, such as Xpert MTB/RIF, can detect RR-TB, people with RR-TB also need DST for SLIDs and FLQs to determine which medicines will be effective, and to tailor their treatment accordingly.

The global TB community applauds the development of new diagnostic tools, but these must be accompanied by programmes that implement them. A number of studies and programmatic evaluations have found that Xpert testing alone does not increase the number of people who start on treatment.[12]

HANIF, AN XDR-TB PATIENT, IN THE CLINIC WAITING AREA, MUMBAI, INDIA.

KEY DIAGNOSIS POLICIES

COUNTRY	Xpert MTB/RIF is the initial TB diagnostic test for adults and children being investigated for TB	TB-LAM is used to diagnose TB in PLWHA with CD4 ≤ 100 µL or seriously ill	First-line DST (rifampicin and isoniazid) is done for all RR-TB cases or for people at risk of DR-TB	Second-line DST (fluoro-quinolones and second-line injectable agents) is done for at least all RR-TB cases
Afghanistan	●	●	●	●
Armenia	● [a]	●	●	●
Bangladesh	●	●	●	●
Belarus	● [b]	●	●	●
Brazil	●	●	●	●
Cambodia	●	●	●	● [c]
CAR	●	⊗	○	?
China	●	●	●	●
DRC	●	●	●	● [c]
Ethiopia	●	●	●	○
Georgia	●	●	●	●
India	●	●	○	○
Indonesia	○	●	?	○
Kazakhstan	●	●	●	●
Kenya	○	●	●	○
Kyrgyzstan	○ [d]	●	○	○
Mozambique	○	●	○	● [e]
Myanmar	●	●	○ [f]	● [f]
Nigeria	○	●	●	⊗
Pakistan	●	●	●	?
PNG	○	●	○	○
Philippines	●	●	○	○
Russian Fed.	○ [g]	●	●	○
South Africa	●	●	●	●
Swaziland	●	●	●	●
Tajikistan	○	●	○	○
Ukraine	●	●	●	●
Viet Nam	●	●	●	●
Zimbabwe	●	⊗	●	●

LEGEND

Is this policy in place at the national level? ● Yes ● No ? Unknown

If Yes, is the policy being implemented? ● Yes ○ Yes, but not widely ⊗ No ? Unknown

(a) The initial diagnostic test is microscopy, but regardless of microscopy result, every person to be evaluated for TB is tested with Xpert. **(b)** Part of an initial diagnostic package of tests. **(c)** Only select groups of patients are eligible. **(d)** At facilities that offer DR-TB regimens with BDQ or DLM. **(e)** No, but second-line DST is available at National Reference Lab. **(f)** Implementation of the 2017 guidelines is expected for the second half of 2017. **(g)** Xpert is part of a package of diagnostic tools; other diagnostic tests can be used, including other rapid molecular methods.

Rapid molecular testing

In 2010, the Xpert MTB/RIF test was hailed as a revolutionary advance in public health. It can diagnose TB and detect resistance to rifampicin (a powerful first-line drug) in less than 2 hours. In South Africa, MSF has documented that using Xpert MTB/RIF reduced time to initiation of RR-TB treatment from over 70 days to just 6 days.[13] This rapid turnaround time makes it possible to start TB treatment right away, thereby lowering the the risks of loss to follow-up and ongoing transmission.

In 2010, WHO endorsed Xpert MTB/RIF;[14] in 2011, WHO issued a policy statement recommending it as the initial diagnostic test for presumptive MDR-TB or HIV-associated TB in adults.[15] In 2013, WHO expanded its recommendation to include children, adding that Xpert MTB/RIF may be used as an initial diagnostic test for adults and children with signs and symptoms of TB (instead of smear microscopy and culture).[16] In March 2017, WHO recommended a next-generation assay, Xpert MTB/RIF Ultra, which uses the same equipment as Xpert MTB/RIF and will gradually replace it.[7] The Ultra assay is more sensitive than Xpert MTB/RIF for diagnosing smear-negative, culture-positive TB, paediatric and extrapulmonary TB, and HIV-associated TB.[7] However, the specificity of Xpert Ultra is somewhat lower than that of the previous Xpert MTB/RIF, which could lead to overtreatment, particularly in patients with a history of TB.[5] The Global Laboratory Initiative (GLI), a working group of the Stop TB Partnership, has developed practical guidance for an easy transition to Xpert Ultra,[17] and WHO is planning to release policy recommendations for Xpert Ultra in 2018.

Cepheid is developing a new system, Xpert Omni, a small, portable, battery-operated instrument that can be used in remote rural settings. The Omni will be able to run Xpert MTB/RIF and Ultra cartridges, and other Xpert disease-specific cartridges. The cost of the one-module Omni model is expected to be around US$ 2,895[18] versus the US$ 17,000 reduced price for the current four-module Gene Xpert model. The Omni is expected to be available by the end of 2017.

FINDINGS:

- Out of the 29 countries for which information was provided, 52% (15) of countries (Armenia, Belarus, Brazil, Georgia, Indonesia, Kenya, Kyrgyzstan, Mozambique, Nigeria, PNG, Russian Federation, South Africa, Swaziland, Tajikistan and Zimbabwe) recommend the use of Xpert MTB/RIF as the initial diagnostic test for all people (See table 1 for details);

- Xpert MTB/RIF is recommended as the initial diagnostic test for high-risk groups (adults and children at risk for DR-TB and HIV-associated TB) in 97% (28) of countries, but only 54% (15/28) of these countries have implemented this policy on a wide scale.

TABLE 1: XPERT MTB/RIF POLICIES

Xpert as the initial diagnostic test for all people to be evaluated for TB	Xpert as the initial diagnostic test only for high-risk groups
Armenia, Belarus, Brazil, Georgia, Indonesia, Kenya, Kyrgyzstan, Mozambique, Nigeria, PNG, Russian Federation, South Africa, Swaziland, Tajikistan, Zimbabwe	Afghanistan, Armenia, Bangladesh, Belarus, Brazil, Cambodia, CAR, DRC, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Myanmar, Nigeria, Pakistan, PNG, Philippines, Russian Federation, South Africa, Swaziland, Tajikistan, Ukraine, Viet Nam, Zimbabwe

Xpert MTB/RIF implementation

The 2017 GLI specifies the use of Xpert MTB/RIF as part of the preferred TB diagnostic algorithm.[19] However, some high-burden countries still use smear microscopy as the initial diagnostic test, even though it is less sensitive for people living with HIV/AIDS, children and people with extrapulmonary TB – and it cannot detect drug resistance.[20]

Rolling out Xpert MTB/RIF requires more than simply purchasing the device and securing a sustainable source for supplies. Sites need a stable power supply and may require air conditioning, as well as room to store equipment.[10] The devices must be checked, calibrated and repaired, staff must be trained to use them and quality assurance measures must be in place to monitor and evaluate the system.

XPERT MTB/RIF IMPLEMENTATION IN CAMBODIA

Xpert MTB/RIF is recommended as the initial diagnostic test to replace smear microscopy, but the cost makes it important to prioritise certain groups for testing. Cambodia was one of the few early adopter countries. It began using Xpert MTB/RIF as an initial diagnostic test in 2012, as part of TB REACH's* active case finding work.[12] Although Xpert MTB/RIF is highly sensitive, studies have shown that just using it alone will not increase the number of people treated for TB.[12] Therefore, CENAT (The Cambodian NTP) and its partners used Xpert MTB/RIF in a series of outreach efforts that identified people with TB who routine systems were not finding. Using equipment and knowledge from TB prevalence surveys, outreach workers conducted awareness-raising and set up mobile community camps. They screened historical household contacts (the household contacts of people with TB for a 2-year period), the elderly and people living in poverty pockets, using a progressive algorithm of chest x-ray and Xpert MTB/RIF testing.[21,22] The active outreach approaches found people earlier in their disease progression and in greater numbers than routine care. These efforts show the utility and cost-effectiveness of using Xpert MTB/RIF as part of active case finding interventions, instead of only placing it in a health facility where it will be unlikely to reach those who are missed.[23]

* TB REACH funds innovative service delivery strategies to improve TB detection and treatment.

FINDINGS:

- The use of Xpert MTB/RIF as the initial diagnostic test for all people has been widely implemented only in 47% (7/15) of countries: Armenia, Belarus, Brazil, Georgia, South Africa, Swaziland and Zimbabwe.

See table 2 for implementation levels of Xpert MTB/RIF policies.

TABLE 2: IMPLEMENTATION OF XPERT MTB/RIF POLICIES

Implementation of "Xpert for all"	Implementation of "Xpert for high-risk groups"
Armenia, Belarus, Brazil, Georgia, South Africa, Swaziland, Zimbabwe	Armenia, Bangladesh, Belarus, Brazil, Cambodia, Ethiopia, Georgia, Kazakhstan, Myanmar, Nigeria, South Africa, Swaziland, Ukraine, Viet Nam, Zimbabwe
Indonesia, Kenya, Kyrgyzstan, Mozambique, Nigeria, PNG, Russian Federation, Tajikistan	Afghanistan, CAR, DRC, India, Indonesia, Kenya, Kyrgyzstan, Mozambique, Pakistan, PNG, Philippines, Russian Federation, Tajikistan

LEGEND Yes Yes, but not widely

BACTERIA CULTURE TUBES USED FOR DIAGNOSING TB IN THE NATIONAL TB REFERENCE LABORATORY OF THE GOVERNMENT HOSPITAL, MBABANE, SWAZILAND.

COSTS ASSOCIATED WITH XPERT MTB/RIF

In August 2012, after collective price negotiations between the Bill & Melinda Gates Foundation, the United States President's Emergency Plan for AIDS Relief (PEPFAR), the United States Agency for International Development (USAID), UNITAID and Cepheid (the manufacturer of Xpert MTB/RIF), the price of cartridges was reduced from US$ 16.86 to US$ 9.98 in 145 high TB burden and developing countries.[24] These reduced prices are accessible only to public facilities in eligible countries.[25] The concessionary price for the machine itself (a standard four-module GeneXpert instrument with a desktop) is US$ 17,000 and includes a 2-year warranty.

Cartridge prices represent a large expense, and there are additional costs for salaries, training, equipment, repairs, module calibration and maintenance, and general laboratory operation. These costs can vary greatly by country. For example, detailed costing analyses for India and South Africa suggested that the overall costs per Xpert MTB/RIF test were US$ 11.60 and US$ 14.90, respectively.[26,27]

Although many researchers have demonstrated that Xpert MTB/RIF implementation is cost-effective,[28] additional domestic and donor funding is required to make it available to all people. According to WHO, changing from current diagnostic tests to "Xpert for all" will create a 38% increase in annual costs for the 30 high TB burden countries;[11,28] this figure does not include additional costs for distribution, customs and equipment maintenance. TB funding often strongly depends on international donors. For example, in 2016, international donors provided 75% of the available funding for national TB plans in 25 high-burden countries (except for Brazil, Russian Federation, China, India and South Africa, which rely mainly or totally on domestic funding),[1] and more than three-quarters of these countries reported a funding gap for 2016.[1]

Governments and global health actors are exploring strategies to further reduce the price of Xpert MTB/RIF through renting and leasing equipment instead of purchasing it; integrating maintenance and service costs into the test price instead of using standalone services and maintenance contracts; and negotiating volume-based pricing, including across countries and pathologies (e.g., cartridges for HIV, hepatitis C virus [HCV] and Human pampillomavirus [HPV]).

SPOTLIGHT – SCALE-UP OF MOLECULAR TESTING IN INDIA

India has the world's highest TB burden; in 2015, 2.8 million people fell ill with TB and 480,000 people died from it.[1] Smear microscopy is often used as the initial diagnostic test in the public sector, and in the private sector where up to 70% of people are treated, delays in diagnosis and treatment initiation are common.[29,30]

A study using Xpert MTB/RIF (referred to as CB-NAAT) for initial diagnostic testing in 18 sub-district-level TB programmes reported an over 5-fold increase in the detection of rifampicin resistance.[31] However, India's public-sector programmes still use smear microscopy as the initial diagnostic test, except in people with presumptive DR-TB or extrapulmonary TB, children, and people living with HIV. Access to Xpert MTB/RIF is limited to India's reference or tertiary hospitals, which increases the risk of loss to follow-up before a confirmed diagnosis.[32]

A 2015 review of India's National Strategic Plan (NSP) reported that many key performance indicators had not been achieved, and that uptake of Xpert MTB/RIF was slow. The review recommended costing, fully funding and implementing universal DST by 2019 (and by 2015 in settings with a high burden of MDR-TB).[33]

Currently, there are more than 735 Xpert MTB/RIF machines in the country NSP 2017-2025. By 2019, the country's Central TB Division plans to deploy 1,019 GeneXpert machines and a network of at least 120 labs for DST, with the goal of treating at least 60,000 people with MDR-TB each year. Currently, phenotypic DST for FLQs and SLIDs is being conducted in 26 laboratories and genotypic testing using SL LPA is planned in 54 laboratories; training is completed and it will be rolled out in 2017.[34]

Drug-sensitivity testing (DST)

Drug-resistant forms of TB can be directly transmitted,[35] and will continue to spread unless people are treated and cured. By 2040, DR-TB is more likely to be directly transmitted than a consequence of unsuccessful treatment.[34] DST is essential to stopping TB, since people who are not properly diagnosed cannot be effectively treated.

DST is also key to implementing the 2016 WHO recommendation for a shorter treatment regimen (9 to 12 months) for RR- and MDR-TB in certain circumstances. Eligibility is based on a person's TB treatment history and results from DST for resistance to FLQs and SLIDs, when available (or, in the absence of DST, use of surveillance data on prevalence and types of resistance in the area).[36]

Universal access to initial testing for rifampicin resistance will facilitate shorter treatment. Implementing the shorter regimen can spare people being treated for DR-TB from months of toxic treatment, financial and other hardships, and save money for TB programmes. Second-line DST using LPA is ideal before starting the shorter treatment regimen for MDR-TB, but WHO guidance also allows for culture-based DST and starting the shorter treatment without DST if it is unavailable.[37]

The 2016 GLI framework of indicators and targets for laboratory strengthening under the End TB Strategy helps to pave the way for widely accessible drug-resistance testing and shorter treatment, by calling on countries to adopt universal RIF-DST for all people with bacteriologically confirmed TB and subsequently, DST for at least FLQs and SLIDs for all people with RR-TB.[6] Countries with a high burden of MDR-TB should implement this strategy by 2018, while all other countries should adopt it by 2020.[6]

DST methods include genotypic diagnostics (such as Xpert MTB/RIF and LPAs for rapid rifampicin- and isoniazid-resistance testing); testing for resistance to SLIDs and FLQs; and phenotypic diagnostics (including culture-based methods for TB detection, followed by DST). Both LPA and culture are labour-intensive and require substantial lab infrastructure; results from phenotypic testing methods can take up to several weeks.

FINDINGS:

- Rifampicin resistance testing for all people with bacteriologically confirmed TB was recommended in the guidelines in 72% (21) of countries. It has been widely implemented in 48% (10) of these countries;
- Second-line drug sensitivity testing DST (at least for SLIDs and FLQs) at least for all RR-TB cases is recommended in guidelines in 83% (24) of countries. It has been widely implemented in 50% (12/24) of these countries;
- Universal DST (DST for rifampicin resistance [RIF-DST] for all people with bacteriologically confirmed TB followed by second-line DST for FLQs and SLIDs for all people with RR-/MDR-TB) is recommended in guidelines in 62% (18) of countries. Universal DST has been widely implemented in 50% (9/18) of these countries. The countries that are widely implementing universal DST are: Armenia, Belarus, Brazil, Georgia, Kazakhstan,South Africa, Swaziland, Ukraine and Zimbabwe.

See table 3 for more information on access to DST across the 29 countries surveyed for this report.

TABLE 3: DRUG-SENSITIVITY TESTING (FOR ALL PEOPLE WITH BACTERIOLOGICALLY CONFIRMED TB)

	Policy recommends that RIF-DST is conducted for all bacteriologically confirmed TB patients	Policy recommends DST for SL-DST (at least FLQ and SLID) is done for at least all RR-TB cases	Policy recommends that RIF-DST for all bacteriologically positive and at least FLQ and SLID for all RR-TB cases is conducted (universal DST)
Countries that have the policy in place	Armenia, Belarus, Brazil Cambodia, China, Georgia, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Myanmar, Nigeria, Pakistan, PNG, Russian Federation, South Africa, Swaziland, Tajikistan, Ukraine, Zimbabwe	Afghanistan, Armenia, Belarus, Brazil CAR, China, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Nigeria, Pakistan, PNG, Philippines, Russian Federation, South Africa, Swaziland, Tajikistan, Ukraine, Viet Nam, Zimbabwe	Armenia, Belarus, Brazil, China, Georgia, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Nigeria, Pakistan, PNG, Russian Federation, South Africa, Swaziland, Tajikistan, Ukraine, Zimbabwe
Implementation level			
●	Armenia, Belarus, Brazil, Georgia, Kazakhstan, Myanmar, Russian Federation, South Africa, Swaziland, Ukraine, Zimbabwe	Afghanistan, Armenia, Belarus, Brazil, China, Georgia, Kazakhstan Kyrgyzstan, South Africa, Swaziland, Ukraine, Viet Nam, Zimbabwe	Armenia, Belarus, Brazil, Georgia, Kazakhstan, South Africa, Swaziland, Ukraine, Zimbabwe
●	Cambodia, China, Kenya, Kyrgyzstan Mozambique, Nigeria, Pakistan, PNG, Tajikistan	Ethiopia, India, Indonesia, Kenya, Kyrgyzstan, Mozambique, PNG, Philippines, Russian Federation, Tajikistan	China, Kenya, Kyrgyzstan, PNG, Russian Federation, Tajikistan
✕		Nigeria	
?	Indonesia	CAR, Pakistan	Indonesia, Pakistan

LEGEND ● Yes ● Yes, but not widely ✕ No ? Unknown

TB-LAM for diagnosing TB in people living with HIV

HIV increases vulnerability to, and morbidity and mortality from TB. HIV-positive people with latent TB infection are 26 times more likely to develop active TB than HIV-negative people.[38] TB is the leading cause of death among people living with HIV. In 2015, 400,000 people living with HIV died from TB co-infection.[1]

Given the prevalence and severity of TB co-infection among people living with HIV, WHO recommends that HIV-positive people be screened for active TB at each visit to a health care facility.[39] But TB can be difficult to diagnose in people living with HIV. More than 50% of people with TB/HIV co-infection are smear negative due to their inability to produce sputum, low sputum bacillary loads or because they have extrapulmonary TB.[40]

Simple, more accurate tests are needed to diagnose TB co-infection in people living with HIV. Although it is not recommended as a standalone test – or for HIV-negative people – TB-LAM, a rapid, point-of-care urine test, detects lipoarabinomannan (LAM), which is a marker of active TB disease and increased mortality risk during TB treatment in HIV-positive people.[41] TB-LAM is most sensitive in HIV-positive people who are seriously ill and/or have low CD4 cell counts. Therefore, WHO recommends TB-LAM specifically for helping to diagnose active TB in HIV-positive adults with TB signs and symptoms and a CD4 cell count of ≤100 cells/μL, or those who are very sick, at any CD4 cell count.[42] Since it delivers results in less than 30 minutes and is priced between US$ 2.66[43] and US$ 3.50 per test,[44] TB-LAM can be a valuable tool for identifying people with the most urgent need for TB treatment.

FINDINGS:

- Among all of the countries surveyed, only CAR and Zimbabwe have a guideline on the use of TB-LAM for diagnosing TB in people living with HIV/AIDS;
- A number of countries (Russian Federation, South Africa and Viet Nam) use TB-LAM in selected facilities, and Kenya and Mozambique use it for research.

SPOTLIGHT – MSF USE OF TB-LAM

MSF has conducted operational research in three countries, studying the diagnostic value and feasibility of TB-LAM under routine programmatic conditions in Kenya,[45] Malawi[46] and Mozambique. In Kenya, MSF studied TB diagnostics in 474 HIV-positive adults with TB symptoms, who were either outpatients or hospitalised in the Homa Bay Country Hospital. TB-LAM was added to combinations of other tests in order to study the incremental 'diagnostic yield' (the proportion of people with bacteriologically confirmed TB who were detected by adding TB-LAM to different diagnostic algorithms).

Regardless of the algorithm used, adding TB-LAM testing increased the number of people with bacteriologically confirmed TB who were diagnosed; for example, adding TB-LAM to diagnosis based on clinical signs and microscopy increased the diagnostic yield among 156 people with confirmed TB by nearly 20%. Using a diagnostic algorithm of clinical signs plus Xpert MTB/RIF identified 74.4% of people with TB; this diagnostic yield increased by 13% when TB-LAM was added. Importantly, using clinical signs and TB-LAM had a diagnostic yield similar to an algorithm based on using clinical signs plus Xpert MTB/RIF testing (76.9% vs. 74.4%, respectively).[45]

In addition to the diagnostic benefit, feasibility studies found that TB-LAM testing had significant operational advantages. Implementing TB-LAM testing required only 1.5 to 4 hours of training, after which users found it very easy to use the test.[45] Most importantly, under routine conditions, TB-LAM results were available within 2 hours, while microscopy and Xpert MTB/RIF results were available within 2 days, and x-ray results after an average of 4 days.[45] Using TB-LAM instead of routinely conducted tests would allow for same-day TB treatment initiation and reduce loss to follow-up, since patients would be spared the need for additional clinic visits.

Urine testing has a major advantage over sputum. In Malawi, Mozambique and Kenya, more than 99% of HIV-positive participants in the studies were able to provide urine samples, while only 75% were able to produce sputum samples.[45,46,47]

Based on their findings, the authors recommended TB-LAM for all hospitalised patients with symptoms of TB, and in ambulatory settings for severely ill patients with low CD4 counts. Using TB-LAM would expedite treatment initiation, especially in patients at high risk of death, in all settings, including those with access to immediate Xpert MTB-RIF results; TB-LAM would be particularly useful in settings where Xpert MTB/RIF is not available or results are delayed.[44,45,46]

WHAT NEEDS TO HAPPEN

- **Rapid diagnostic testing:** Countries need to be bold by accelerating access and increasing their capacity to universally provide Xpert MTB/RIF testing for all instead of microscopy, with urgent prioritisation of key populations (people at risk for DR-TB, people living with HIV, and children). Lessons learned from successful interventions to improve TB case detection, such as a number of TB REACH initiatives, should be scaled up to reach people missed by routine screening.

- **Drug-sensitivity testing:** Countries and partners need to scale up access to DST, including RIF-DST and DST for SLIDs and FLQs.

- **TB-LAM:** Countries should scale up the use of TB-LAM, using donor funding and technical support, so that it can be implemented, particularly in settings with a high prevalence of HIV.

- **Procurement:** Countries and global actors should continue to explore different procurement strategies for Xpert (such as reagent rental agreements and leasing) and pricing schemes that leverage markets across countries and diseases (e.g., bundling TB, HIV and HCV needs) to negotiate volume-based prices for equipment, reagents, and service and maintenance contracts.

- **Quality-assured laboratory:** Countries and their partners need to make a consistent effort to ensure a holistic scale-up approach that includes quality-assured diagnostic tools and laboratory networks, as well as patient treatment and care.

- **Funding:** Domestic and international donors must increase funding in high-burden countries to scale up access to quality-assured diagnostics.

- **R&D:** Increased research and development (R&D) is urgently needed to develop a novel rapid, TB diagnostic test that is readily available at the point of care for US$ 5 or less.

MSF TB DOCTOR VERONIKA EXAMINES 66-YEAR-OLD SAMUEL IN MATSAPHA, MANZINI REGION, SWAZILAND.

Sydelle Willow Smith

SIBONGILE, A DR-TB PATIENT, LEAVES THE TOWN CLINIC FOLLOWING HER CONSULTATION IN KHAYELITSHA, SOUTH AFRICA.

MODELS OF CARE

KEY FINDINGS

- Initiation of DS-TB treatment at the primary health care level is recommended in the guidelines in 83% (24) of countries. In Armenia, the majority of people start DS-TB treatment at the central level hospital or at regional DS-TB units;
- Routine hospitalisation for the treatment of DS-TB is required in 21% (6) of countries;
- Initiation of DR-TB treatment at the district level is recommended in the guidelines in 66% (19) of countries;
- Routine hospitalisation for the treatment of DR-TB is required in 35% (10) of countries;
- The HIV 'test and start' antiretroviral therapy (ART) policy (providing antiretrovirals [ARVs] for all HIV-positive people) has been adopted by only 38% (11) of countries, and implemented widely in only 73% (8/11) of these countries.

BACKGROUND

A patient-centred approach is one of the important underlying principles of the End TB Strategy. Such an approach demands respect for people with TB, and for them to be treated as individuals and partners in their own TB care.[48]

Keeping people with TB at the centre of their TB and DR-TB treatment is essential to successful treatment. Over 50 years ago, WHO recognised that resources were best used for ambulatory TB care, instead of hospital beds.[49] A WHO strategy recognised that TB treatment must be expanded to the "poorest urban and rural settings involving providers who practice close to where patients live."[50]

Ambulatory MDR-TB care is as effective as – and significantly less expensive than – hospitalisation. A single day in the hospital can cost up to 15 times more than an outpatient visit.[51] Compulsory hospitalisation can facilitate the spread of DR-TB because of lengthy delays prior to treatment initiation and poor infection control in hospitals.[52,53]

Decentralising TB and MDR-TB treatment relieves a deadly bottleneck by expediting time to treatment initiation; moreover, patients prefer it.[54]

HIV significantly increases the risk for and worsens the course of TB. TB is the leading cause of death among people living with HIV; in 2015, 400,000 people living with HIV died from TB.[1] However, the deadly link between TB and HIV can be broken through a 'one-stop shop' that facilitates testing, care and treatment for HIV and TB in one place, and makes it faster and easier for patients to access life-saving treatment for both. ART, which is now recommended for all HIV-positive people of any age and regardless of CD4 cell count,[5] and TB preventive therapy, which is also recommended for HIV-positive people in high-prevalence and resource-limited settings,[55]are protective against TB, especially in combination.[56]

LEVELS OF CARE

TB services can be provided at different levels: community-based, where household care is delivered by community health workers or others at local health posts; at the primary health care level, such as at clinics or other facilities; at the district level, such as at hospitals or other health centres; at the tertiary level, which is often a provincial or regional hospital or other facilities; and at the national level, where hospitals or other facilities offer expert care.

TB treatment initiation

Decentralising HIV treatment initiation and task-shifting to nurses and community health care workers has increased ART access and uptake, and improved adherence and treatment outcomes.[57] The same is true for TB: decentralising treatment is preferable for people with TB who wish to remain in their communities; it has improved treatment outcomes and lowered costs per patient.[58,59,60,61]

FINDINGS:

- DS-TB treatment can be started at the primary health care level in 83% (24) of countries. This policy has been widely implemented in 83% (20/24) of these countries;
- DS-TB treatment is started at the primary health care level in all of the African countries surveyed for the report;
- According to national guidelines, nurses and health care workers other than doctors can start adults on DS-TB treatment in 52% (15) of countries;
- Of the eight Eastern Europe and Central Asian (EECA) countries featured in the report, only Kazakhstan, Kyrgyzstan and Tajikistan can start DS-TB treatment at the primary health care level.

KEY MODELS OF CARE POLICIES

COUNTRY	DS-TB treatment is started at the primary health care level*	DR-TB treatment is started at the district level*	Hospitalisation is NOT required for DS-TB treatment*,◆	Hospitalisation is NOT required for DR-TB treatment*,◆	ARV treatment is offered to all PLWHA ('test and start')
Afghanistan	Yes	No	Yes	Yes	No
Armenia	No [a]	No [a]	No	No [a]	No
Bangladesh	Yes	Yes, but not widely	Yes	No	No
Belarus	No	No	No [a]	No [a]	No
Brazil	Yes	No	Yes	Yes	Yes
Cambodia	Yes	No	Yes	No	Unknown
CAR	Yes	No	Yes	Yes	No
China	Yes	No	Yes	No	Yes
DRC	Yes	Yes	Yes	Yes	Yes
Ethiopia	Yes	Yes	Yes	Yes	Yes
Georgia	No [b]	No [a]	No	No	Yes
India	Yes	Yes	Yes	Yes	No
Indonesia	Unknown	Unknown	Yes	Yes	No
Kazakhstan	Yes	Yes	No	No	No
Kenya	Yes	Yes	Yes	Yes	Yes
Kyrgyzstan	Yes, but not widely	Yes	No	No	No
Mozambique	Yes	Yes, but not widely	Yes	Yes	Yes, but not widely
Myanmar	Yes	Yes, but not widely	Yes	Yes	No
Nigeria	Yes	Yes	Yes	Yes	No
Pakistan	Unknown	No	Yes	Yes	No
PNG	Yes	No	Yes	Yes	Yes
Philippines	Yes	Yes, but not widely	Yes	Yes	No
Russian Fed.	No	Yes [c]	No	No	No
South Africa	Yes	Unknown	Yes	Yes	Yes, but not widely
Swaziland	Yes	Yes	Yes	Yes	Yes
Tajikistan	Yes, but not widely	Yes, but not widely	Yes	Yes	No
Ukraine	No	No	Yes	Yes	No
Viet Nam	Yes	Yes	Yes	No	No [d]
Zimbabwe	Yes	Yes	Yes	Yes	No

LEGEND **Is this policy in place at the national level?** Yes · No · Unknown — **If Yes, is the policy being implemented?** Yes · No · Unknown · Yes, but not widely

(*) Including smear-positive individuals. In some countries exceptions are made for people who are smear-negative and on a case by case basis. **(◆)** The implementation of the policy was not assessed for the hospitalisation questions. **(a)** Except for people who are smear-negative and on a case by case basis. **(b)** Patient receives a prescription at TB facilities. **(c)** DR-TB treatment can be started and dispensed from the district level, but only after decision and prescription from the regional TB committee. **(d)** Test and start in mountainous, coastal and remote provinces.

SPOTLIGHT – TB ADHERENCE COUNSELLING

Adherence to 6–24 months of TB treatment is essential to its success. To improve adherence, people with TB should be provided with education, support and counselling. Much has been learned from treating HIV, which requires lifelong adherence to antiretroviral treatment. Lay counsellors, community health workers and adherence clubs (groups of people living with HIV who are on treatment and virally suppressed meet to support each other, undergo routine monitoring and seek health care if needed) have increased uptake of and retention in HIV treatment programmes, while freeing up doctors and nurses to focus on sicker patients.[62,63]

Similar programmes and services are essential for people being treated for TB. The End TB Strategy considers adherence counselling key to the implementation of patient-centred treatment for all forms of TB.[64] Community health workers play a critical role in TB treatment outcomes; as the link between patients and health care systems, they can improve DR-TB treatment adherence[65,66] and facilitate the decentralisation of DR-TB treatment.

During DR-TB treatment, patient support is "as essential as the pills they take every day",[67] since patients must take up to 15 pills each day, and endure serious side effects and months of painful injections – sometimes for 2 years – with a high risk of treatment failure.

To encourage collaboration between clinicians, nurses and counsellors, to support adherence, and to optimise treatment outcomes, MSF developed a comprehensive counselling toolkit for decentralised DR-TB treatment in 2014.[68] Structured, patient-centred counselling covers the continuum from diagnosis to treatment completion or failure; patients learn about why and when to take medication, side effects, how to address adherence barriers and other challenges, and how to get support and set personal goals.[53]

DR-TB treatment initiation

In 2015, only 1 in 5 people estimated to have MDR-TB made it through the diagnostic and treatment pathway.[50] Lengthy travel to specialised facilities, stigma, and bureaucratic health care systems cause delays in treatment initiation and high rates of loss to treatment.[69]

In Viet Nam, decentralising MDR-TB care and treatment significantly increased the number of people starting treatment, from 97 in 2010 to 1,380 by 2012.[70] Overall, 73% were cured (versus the global average of 50%)[1]; treatment was unsuccessful for 6%, 8% died, and 13% were lost to follow-up.[70]

FINDINGS:

- DR-TB treatment is started at the district level in 66% (19) of countries;
- Only 58% (11/19) of these countries have implemented the policy widely: DRC, Ethiopia, India, Kazakhstan, Kenya, Kyrgyzstan, Nigeria, Russian Federation, Swaziland, Viet Nam and Zimbabwe.

See table 4 for the lowest level health care facility providing DR-TB treatment in seven countries.

TABLE 4: LEVEL OF HEALTH CARE FACILITY OFFERING DR-TB TREATMENT

Country	Lowest level of health care facility at which DR-TB treatment can be started and dispensed
Armenia	Majority of DR-TB cases start treatment from National Tuberculosis Control Centre (NTCC) DR-TB unit (central level)
Cambodia	Started at provincial level, continued at district level
CAR	National
China	Prefecture level (city) and then transferred to county level
Georgia	Central level
Pakistan	Programmatic Management of DR-TB (PMDT) sites (provincial level)
PNG	Provincial hospital

SPOTLIGHT – MANGALISO'S STORY: DECENTRALISED DR-TB TREATMENT IN SWAZILAND

Mangaliso Motsa was diagnosed with DR-TB in 2016 and referred to the TB hospital in Moneni. He started treatment on the day he was admitted to the hospital and spent 3 weeks there. After being discharged, he continued his treatment at home, but still visited his local clinic in Matsapha for daily injections for several months.

Each month, he visits the hospital for a medical consultation with his doctor and to have his TB medicines refilled. He has completed the daily injections and expects to finish his treatment later in 2017. The support he has received has helped him to successfully follow his treatment from home – and to start a new life after treatment.

"At the start I suffered a lot of side effects: I developed a skin rash and the colour of my eyes changed. Sometimes I still feel tired and lethargic or dizzy. The support group of other patients that I belong to has been very helpful. They helped me to understand and tolerate the side effects I was experiencing through sharing their own experiences with me.

The support I receive from the hospital makes it easy for me to stay on treatment. On my refill dates, I also receive a food voucher and transport allowance. I had no excuse not to go for my injections or stick to my treatment.

I am a lot better now, even the side effects have stopped. I started feeling a change in my health within the first 3 weeks of treatment. Now, I feel healthy and I am able to live a normal life.

> I live on my own in a rented flat not far from my home. The hospital told me that I would have to stay separately to avoid infecting other members of my family. So I moved out to this flat.

I think it's better to receive treatment from home. The quality of life is much better. Being admitted in hospital is very lonely and this can cause depression. You miss your friends and family, and because you are idle you tend to think of a lot of stressful things.

I was able to do some odd jobs even during my treatment – something I wouldn't have been able to do if I was treated in hospital.

A little while after I finished my injections, I asked my doctor if I could go back to work. He said I could, so I went back to my work as a sugar packer in Matsapha. I was lucky that I did not lose my job. Many patients lose their jobs."

Ambulatory care

WHO recommends expanded services and ambulatory care for people with DR-TB, reserving hospitalisation only for people who are very ill. In the past, people with DR-TB faced up to 8 months of mandatory hospitalisation. At the time, this approach was thought to limit transmission, ensure that patients were taking their medication, and allow for management of adverse events. But limited space delayed hospital-based treatment initiation; a study in 2007 found that, in some settings, newly diagnosed DR-TB patients had to wait up to 120 days to start treatment.[71] Furthermore, poor infection control in hospitals can actually facilitate the spread of DR-TB to other patients and health care workers.[51,52] In addition, the high cost of hospitalisation is not feasible for resource-limited countries, where a day in the hospital costs 2 to 15 times more than an outpatient visit.[53]

The first proof that home-based TB care was effective came from a study among people with DS-TB conducted over 50 years ago. The study found that people treated at home had similar outcomes to hospitalised patients,[49] despite poorer nutrition, overcrowding and more advanced TB.[72] Home-based treatment was not found to increase transmission to close contacts.[73] These findings led to a 1964 WHO recommendation that "all financial resources and manpower available for tuberculosis control in developing countries be confined to organizing efficient ambulatory care and not to constructing new beds."[74] Since then, numerous studies have found that hospital-based DR-TB treatment does not result in better outcomes than community-based treatment.[53,75]

Hospitalisation isolates people from their families, who often cannot afford to travel long distances for visits.

Decentralised, ambulatory care allows people to stay among their family and friends, and rely on their encouragement; their families prefer it because they can provide emotional support.[76] Patients, along with their families and communities, believe that psychosocial support associated with home-based care is more conducive to recovery than hospitalisation.[77] Decentralised and ambulatory DR-TB treatment increases case notification rates, speeds up treatment initiation, improves survival and is cost-effective.[13, 78,79]

FINDINGS:

- Routine hospitalisation for the treatment of DS-TB is required in 21% (6) of countries. These include: Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan and Russian Federation;
- Routine hospitalisation for the treatment of DR-TB is required in 35% (10) of countries. These include: Armenia, Bangladesh, Belarus, Cambodia, China, Georgia, Kazakhstan, Kyrgyzstan, Russian Federation, and Viet Nam;
- Of the eight EECA countries featured in the report, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan and the Russian Federation still require hospitalisation for DR-TB treatment;
- Of the nine Sub-Saharan African (SSA) countries featured in the report, none of the countries require hospitalisation for DR-TB treatment;
- Of the five South East Asian (SEA) countries featured in the report, two countries require hospitalisation for DR-TB treatment.

See table 5 for more details.

TEIMURAZ AJIBA, A PATIENT AT THE REGIONAL CENTER OF INFECTIOUS PATHOLOGY, AIDS AND TUBERCULOSIS IN BATUMI, GEORGIA.

TABLE 5: DS-TB AND DR-TB TREATMENT INITIATION POLICIES

DS-TB treatment started at primary health care level	DR-TB treatment started at district level	Hospitalisation required for DS-TB treatment	Hospitalisation required for DR-TB treatment
Afghanistan, Bangladesh, Brazil, Cambodia, China, DRC, Ethiopia, India, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Myanmar, Nigeria, Pakistan, PNG, Philippines, South Africa, Swaziland, Tajikistan, Viet Nam, Zimbabwe	Bangladesh, DRC, Ethiopia, India, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Myanmar, Nigeria, Philippines, Russian Federation, South Africa, Swaziland, Tajikistan, Ukraine, Viet Nam, Zimbabwe	Armenia*, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Russian Federation	Armenia, Bangladesh, Belarus, Cambodia, China, Georgia, Kazakhstan, Kyrgyzstan, Russian Federation, Viet Nam

*preferably as opposed to required

SPOTLIGHT – DECENTRALISATION OF DR-TB TREATMENT IN SOUTH AFRICA

In 2007, MSF, in partnership with the local Department of Health (DoH), piloted a decentralised model of care for all forms of DR-TB in Khayelitsha, South Africa, a township with high rates of HIV, DR-TB and TB/HIV co-infection. Overall, 70% of 1,400 cases of DR-TB diagnosed between 2008 and 2014 were among people living with HIV/AIDS.[54]

Delivering community-based DR-TB treatment and using rapid diagnostics sped up the time from diagnosis to treatment initiation (from 50 to 6 days), boosted patient support, improved survival and lowered costs.[54] Overall, in this decentralised model, 88% of nearly 1,000 people diagnosed with DR-TB between 2009 and 2013 started treatment, versus the national rate of 45%.[54,80] These successes contributed to a 2011 national policy to decentralise DR-TB treatment;[81] however, it is still not standard practice across the country to initiate DR-TB treatment in primary care settings, and patients are waiting for months before being admitted into centralised TB care facilities.[82]

The now DoH-run programme features a network of primary care clinics, a short-term inpatient facility, daily care and home treatment delivery for patients who are too sick to visit their clinic; patient-centred counselling and support, which is intensified for patients who miss clinic visits; weekly or monthly self-administered continuation phase treatment supported by Community Care Workers; and individualised treatment with new and repurposed TB medicines.[54]

Decentralisation has not necessarily improved DR-TB treatment outcomes, although it is likely to reduce direct transmission through early case detection and treatment initiation. From 2007 until 2012, 37% of people with pre extensively drug-resistant (pre-XDR) TB and 26% of people with XDR-TB were cured.[54] The poor outcomes were mainly due to loss to follow-up and the limited effectiveness of treatment for pre-XDR and XDR-TB. These challenges underscore the urgent need for less toxic, more effective and shorter treatment regimens for DR-TB.

Services for people living with HIV

The HIV and TB epidemics fuel one another; each infection worsens the other. HIV increases vulnerability to TB infection by up to 31-fold.[1,4]

Recognising the deadly nature of these co-epidemics, in 2004, WHO released an interim policy on TB/HIV collaborative activities and, in 2012, issued an evidence-based update, emphasising the need to deliver TB and HIV services at the same location and time: the 'one-stop shop'.[83]

WHO now recommends ART for all HIV-positive adults, adolescents, children and infants, at any CD4 cell count[47]; it has recommended TB preventive therapy for all people living with HIV (without signs and symptoms of active TB) since 1998.[84] On their own, both ART and preventive therapy lower the risk for TB; combining them increases protection against TB.[57,85] DR-TB treatment is just as effective for HIV-positive people, provided that they are receiving ART (except among people with ≤100 CD4 cells /µL.[86]

The 'one-stop shop' has been used in South Africa, a country with one of the highest burdens of TB, TB/HIV and MDR-TB in the world.[1] In 2015, 287,224 people in South Africa were diagnosed with TB; 97% of them had been tested for HIV.[1] At one South African township clinic, integrating TB and HIV services increased the likelihood that TB/HIV co-infected patients would start ART by 60% and shortened the time to ART initiation from 147 to 75 days.[87] By contrast, a study conducted in South Africa between 2002 and 2008 found that patients at separate TB and HIV clinics faced significant delays before starting ART. In 2004, South Africa's HIV treatment guidelines recommended ART initiation within 2 weeks of TB treatment in patients with CD4 cell counts of < 50 cells/µL, and within 8 weeks for patients with CD4 cell counts of 50-200 cells/µL; however, during the study, the overall median delay to ART initiation was 95 days after starting TB treatment. This delay was nearly 3 times longer for TB clinic patients than for HIV clinic patients (116 days versus 41 days).[88]

Mathematical modelling has been used to determine the impact of community-based, decentralised TB and HIV interventions in rural South Africa. The model was based on TB and HIV epidemiology and transmission dynamics, and included interactions between TB, HIV and ART. Using this information, the model compared the cumulative incidence of and mortality from HIV and all forms of TB over a decade to projections based on the implementation of single or multiple initiatives (e.g., intensified community-based case finding; Xpert MTB/RIF screening; increased ART coverage; preventive therapy; DR-TB treatment decentralisation; improved first-line TB treatment outcomes).[89] The model found that the full integration and implementation of services would be the most effective.[89]

CELUMUSA HLATSWAKO, AN MSF MOBILE COUNSELLOR, VISITS WINILE, AN XDR-TB PATIENT, AT HOME IN MANZINI REGION, SWAZILAND.

FINDINGS:

- The HIV 'test and start' ART policy has been adopted by only 38% (11) of countries, and implemented widely in only 73% (8/11) of these countries;
- The countries that are widely implementing the 'test and start' policy include: Brazil, China, DRC, Ethiopia, Georgia, Kenya, PNG and Swaziland;
- Of the SEA countries, only Cambodia has a policy in place for 'test and start';
- Of the SSA countries, DRC, Ethiopia, Kenya, Mozambique, South Africa and Swaziland have a policy in place for 'test and start'.

See table 6 for information on the level of integration of TB and HIV services.

SPOTLIGHT – A GUIDE TO THE 'ONE-STOP SHOP'

The 8th edition of MSF's TB/HIV Clinical Guide, released in 2014, provides a comprehensive approach to integrated, co-located TB/HIV care; it is available at: http://samumsf.org/documents/2015/07/msf-hivtb-clinical-guide_2015_english.pdf

TABLE 6: POLICIES FOR INTEGRATION OF TB AND HIV SERVICES

TB treatment can be started in health facilities providing HIV care	HIV treatment can be started in health facilities providing TB care	The same health worker can provide TB and HIV treatment at the primary health care level
Afghanistan, Brazil, CAR, China, DRC, Ethiopia, Georgia, Kenya, Kyrgyzstan, Mozambique, Nigeria, Pakistan, Philippines, PNG, South Africa, Swaziland, Viet Nam, Zimbabwe	Afghanistan, Armenia*, Belarus, CAR, DRC, Ethiopia, Georgia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Nigeria, PNG, Philippines, South Africa, Swaziland, Ukraine, Viet Nam, Zimbabwe	Brazil, CAR, DRC, Indonesia, Kazakhstan, Kenya, Mozambique, Nigeria, Philippines, South Africa, Swaziland, Tajikistan, Viet Nam, Zimbabwe

*Applicable for inpatient TB care facilities and not outpatient TB care facilities

WHAT NEEDS TO HAPPEN

- **Patient-centred:** People receiving TB treatment must be at the centre of their care, and be supported and encouraged as such.
- **Decentralisation:** TB services need to be decentralised to improve access and decrease out-of-pocket costs.
- **Ambulatory:** Compulsory hospitalisation should be replaced with ambulatory care, including for DR-TB. The resulting cost savings could be used to provide support services and community systems that enable communities to provide patient support during ambulatory care.
- **Integrated care:** TB/HIV co-infection is a significant problem in many countries; care and treatment for both should be closely linked in order to support adherence and successful treatment outcomes (e.g., one treatment facility and one medical team).
- **Treatment as prevention:** Given the benefits of ART in reducing TB incidence, morbidity, mortality and transmission, it is imperative – and urgent – for countries with high rates of TB/HIV co-infection to implement ART 'test and start'.

DR IZA JIKIA (LEFT) AND DR NINO DZIDZIKASHVILI (CENTRE) REVIEW A DR-TB PATIENT'S CHEST X-RAY AT THE NATIONAL CENTER FOR TUBERCULOSIS AND LUNG DISEASE IN TBILISI, GEORGIA.

Daro Sulakauri/MSF

TB & DR-TB TREATMENT

KEY FINDINGS

- Increased doses of first-line drugs for children largely reflects the latest WHO guidance in 86% (24/28) of countries;
- The new paediatric TB fixed-dose combinations (FDCs) are the standard of care in 50% (14/28) of countries, but only 29% (4/14) of them have widely implemented them;
- All countries have national treatment guidelines that reflect WHO DR-TB treatment guidelines;
- Bedaquiline is included in the national guidelines for DR-TB treatment in 79% (23) of countries;
- Delamanid is included in the national guidelines for DR-TB treatment in 62% (18) of countries;
- The WHO-recommended 9-month (shorter) MDR-TB treatment regimen is included in the guidelines in 45% (13) of countries. Of the 13 countries recommending its use, 69% (9/13) have implemented it, but not widely.

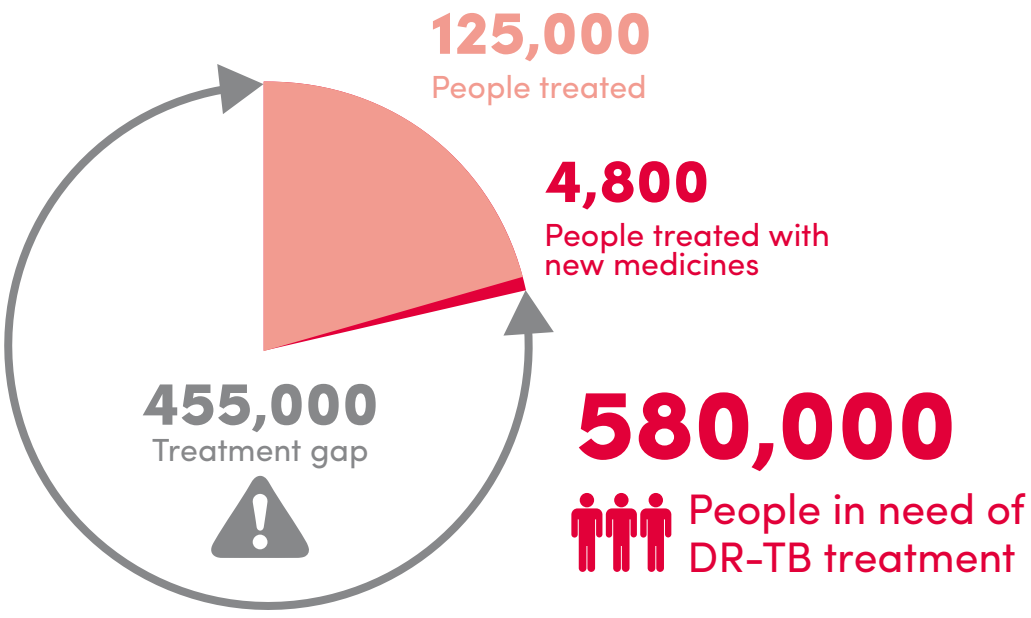
BACKGROUND

TB is the world's deadliest infectious disease. In 2015, it claimed 1.8 million lives,[1] although it is preventable and curable.

TB treatment has evolved from a time when clean air, rest and a good diet offered the best hope for a cure, to today's 6-month regimen for DS-TB (isoniazid, rifampicin, ethambutol and pyrazinamide), and, according to WHO, cures more than 80% of people who complete it.[1] However, there is still ample room for improvement. To achieve the Stop TB Partnership's Global Plan to End TB's 90-90-90 targets, 90% of all people diagnosed with TB must be cured. This calls for the development of shorter, more tolerable, affordable treatments for all forms of TB – and making them universally accessible and delivered with community-based treatment support.

Drug-resistant forms of TB continue to spread and kill. In 2015, WHO estimated that there were 580,000 people with drug-resistant forms of TB; 40% of them (250,000 people) died from DR-TB.[1] Only 132,120 people with DR-TB (less than 25%) were diagnosed, and only 124,990 of them began DR-TB treatment.[1] MDR-TB is more difficult to treat than DS-TB; globally, it is successful for only 52% of people who complete it.[1] To meet the 2035 goals of the End TB Strategy (i.e., to reduce the number of new cases of and deaths from TB by 90% and 95%, respectively, from 2015 levels), safe, effective, tolerable and affordable treatment for drug-resistant forms of TB is urgently needed.

THE TB AND DR-TB TREATMENT GAP



KEY TB & DR-TB TREATMENT POLICIES

COUNTRY	New paediatric TB FDCs are the standard of care	National policy reflects WHO guidance on bedaquiline use for adults	National policy reflects WHO guidance on delamanid use for adults and children	National policy includes the WHO-recommended, 9-month (shorter) MDR-TB treatment regimen
Afghanistan	?	✗	✗	?
Armenia	●	●	●	●
Bangladesh	?	?	?	◐
Belarus	●	●	●	●
Brazil	●	●	●	●
Cambodia	?	?	?	?
CAR	◐	●	●	◐
China	●	●	●	●
DRC	●	◐	●	◐
Ethiopia	✗	●	●	● [a]
Georgia	●	●	✗	●
India	✗	◐	●	●
Indonesia	●	?	●	●
Kazakhstan	●	?	?	●
Kenya	◐	◐	◐	●
Kyrgyzstan	?	◐	✗	◐
Mozambique	?	◐	◐	● [b]
Myanmar	✗	●	●	◐
Nigeria	●	●	◐	●
Pakistan	● [*]	?	?	●
PNG	◐	◐	◐	◐
Philippines	●	◐	◐	?
Russian Fed.	●	●	●	●
South Africa	●	◐	◐	● [d]
Swaziland	●	●	●	◐
Tajikistan	●	● [e]	● [e]	◐
Ukraine	●	●	●	●
Viet Nam	●	●	●	◐
Zimbabwe	●	◐	◐	✗

LEGEND

Is this policy in place at the national level? ? Unknown ✗ No ◐ Yes, but not widely ● Yes

If Yes, is the policy being implemented? ? Unknown ● No ● Yes

(*) The data could not be verified. **(a)** Paediatric guidelines are under revision. **(b)** New DR-TB guidelines in development include shorter MDR-TB regimens per WHO criteria and the NTP plans to enroll the first patients in July 2017. **(d)** New DR-TB guidelines in development include shorter MDR-TB regimens. **(e)** Implementation in pilot sites.

TB treatment in adults

The first pillar of the End TB Strategy is: "Integrated, patient-centred care and prevention."[48] A crucial component of the Strategy is to ensure access to treatment for people with all forms of TB.

Treatment for DS-TB is usually effective, if it is completed without interruption. But side effects, such as vision loss, fever, weakness, nausea, vomiting, and peripheral neuropathy (numbness, tingling or burning sensations in the hands and feet) make adherence challenging, and underscore the need for improved treatment. According to WHO, in 2014, the overall treatment success rate for DS-TB treatment was 83%.[1]

The 2015 *Out of Step* report highlighted key policy gaps in the treatment of DS-TB in adults, some of which remain relevant today.

INTERMITTENT DOSING

In 2015, *Out of Step* reported that India and China were still recommending intermittent dosing (thrice-weekly) during the intensive phase of treatment,[9] even though this approach more than triples drug resistance versus daily treatment.[90] India recently released its National Strategic Plan for TB Elimination, which states that the long-standing recommendation for intermittent dosing has been removed and replaced by daily treatment for all TB patients.[91] The country aims to introduce daily TB treatment across the country in 2017.[92] Except for India and one province of China, none of the surveyed countries use intermittent dosing during the intensive phase of DS-TB treatment.

CATEGORY II TREATMENT

In the past, a combination of medicines known as the 'category II retreatment regimen' was recommended for people with a history of TB treatment.[93] As of May 2017, WHO has recommended that "the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen."[94] WHO also recommended that the empirical MDR-TB regimen should be used if DST is not available to guide the choice of regimen.

FIXED-DOSE COMBINATIONS (FDCS)

TB treatment guidelines from WHO recommend the use of FDCs.[95] They have many advantages: FDCs simplify treatment delivery, improve adherence, and reduce the risk of single-drug stockouts (which can lead to drug resistance and treatment failure); furthermore because dosing is more straightforward, prescription errors are likely to be less frequent with FDCs, and weight-based dosing is easier than with multiple pills.[95]

NISCHAYA, AN XDR-TB PATIENT, PLAYING WITH HER BROTHER AJAY AT HOME IN THE AMBEDKAR NAGAR AREA OF MUMBAI, INDIA.

TB treatment in children

Children are especially vulnerable to TB, particularly if they are malnourished and/or HIV-positive. In 2015, 1 million children fell ill with TB[1], and approximately 210,000 children aged 0–14 died from it.[1]

> The lack of child-friendly drug formulations complicated paediatric TB treatment until December 2015, when FDCs of pleasant-tasting, WHO-recommended paediatric treatment for DS-TB became available.

These replaced older FDCs that had to be crushed to assure weight-based dosing. With the new FDCs, the number of tablets is adjusted based on weight to ensure that children get the right amount of medication.[95] Child-friendly FDCs in the new dosage formulations are available from the Global Drug Facility (GDF) of the Stop TB Partnership.

FINDINGS:

- National treatment guidelines for children reflect the 2014 WHO guidance in 90% (26) of countries. The policy has been implemented widely in 69% (18/26) of them;
- The new paediatric TB FDCs are the standard of care in 50% (14/28) of countries: Afghanistan, Bangladesh, Cambodia, CAR, DRC, Ethiopia, India, Kenya, Kyrgyzstan, Myanmar, Pakistan, PNG Tajikistan and Zimbabwe. Only four countries (DRC, Pakistan, Tajikistan and Zimbabwe) have made FDCs widely available;
- In Brazil, the MoH is currently evaluating the incorporation of paediatric FDCs into its guidelines. In Ethiopia, after having endorsed the previous FDCs (namely, RHZ 60/30/150 and RH 60/30) in 2010, the NTP has decided to transition to the new FDCs in the near future. In South Africa, the new FDCs are not available due to licensing issues;
- First-line drugs and regimens for children largely reflect the latest WHO guidance in 86% (24/28) of countries.

See table 7 for the implementation level of the policy.

TABLE 7: IMPLEMENTATION LEVEL OF PAEDIATRIC TB TREATMENT POLICY

Policy Implementation Level	
According to national guidelines, increased doses of first-line drugs for children are in line with 2014 WHO guidance isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg) ethambutol (E) 20 mg/kg (range 15–25 mg/kg)	● Afghanistan, Armenia, Belarus, Brazil, CAR, DRC, Ethiopia, Georgia, India, Kazakhstan, Kenya, Myanmar, Pakistan, PNG, Tajikistan, Viet Nam, Zimbabwe
	✕ Swaziland
	? Bangladesh, Cambodia, Indonesia, Kyrgyzstan, Mozambique, South Africa

LEGEND ● Yes ✕ No ? Unknown

NONYANYISO, PRE-XDR TB PATIENT, PLAYS WITH HER 8-YEAR-OLD DAUGHTER MINENTLE AT HOME IN KHAYELITSHA, SOUTH AFRICA.

DR-TB treatment in adults

FORMS OF DR-TB

The extent of TB drug resistance varies; WHO has defined different forms of DR-TB to help ensure each type is treated as effectively as possible.

- **Rifampicin-resistant (RR) TB:** When resistance to rifampicin is detected using phenotypic or genotypic methods, with or without resistance to other anti-TB medicines[96]
- **Multidrug-resistant (MDR) TB:** TB that is resistant to rifampicin and isoniazid – two powerful, first-line drugs
- **Pre-XDR-TB:** TB that is resistant to isoniazid, rifampicin and either an FLQ or an SLID
- **XDR-TB:** TB that is resistant to isoniazid, rifampicin, any FLQ and at least one SLID

Drug-resistant forms of TB can be acquired or directly transmitted. Several factors drive the development of TB drug resistance, including misdiagnosis leading to ineffective treatment; prescribing, dispensing or dosing errors; substandard medicines; treatment interruptions or poor adherence; medicine stockouts; insufficient medicine levels in the body; and the inability of medicines to penetrate into TB lesions.[97] According to epidemiological modelling, without changes to current TB prevention and treatment, both direct transmission and rates of MDR- and XDR-TB will continue to increase in high-burden countries.[98]

Drug-resistant forms of TB are more difficult to treat than DS-TB. Until 2016, when WHO released updated guidelines for shorter MDR-TB treatment,[99] treatment could last for up to 24 months,[1] and involved 8 months of painful daily injections and nearly 15,000 pills, many of which have severe side effects. Undergoing DR-TB treatment is an ordeal for patients, their families and governments. People with DR-TB face the risk of permanent deafness and organ damage from their treatment, as well as catastrophic costs, unemployment, and separation from their families and communities. Worse, they may not survive treatment, as treatment success rates are suboptimal: 52% for MDR-TB and 28% for XDR-TB.[1] The price per treatment course ranges from US$ 2,000 to 10 times that amount.[1]

DR-TB treatment is becoming shorter, less toxic and more effective. New TB medicines and treatment strategies can drastically improve the outcome of DR-TB treatment.

Combinations of repurposed medicines that were originally approved for different conditions, companion drugs (that protect against resistance to the main TB medicines), and new TB medicines bring hope to people with all forms of DR-TB.

FINDINGS:

All countries have national treatment guidelines that reflect WHO DR-TB treatment guidelines. However, as illustrated in the following sections, countries must still do much more to reduce death and suffering from DR-TB.

Bedaquiline and delamanid

Newer, highly effective medicines for MDR-TB have been approved, but few people are benefiting from them.

> The first new medicines in nearly 50 years – bedaquiline and delamanid – are only reaching 5% of people who can benefit from these medicines.[100]

In 2016, only 469 people received delamanid outside of a handful of clinical trials or compassionate use programmes; just over 4,300 people received bedaquiline.[101]

By the end of March 2017, 8,195 people had received bedaquiline and 496 had received delamanid, all under programme conditions.[102] Of all high-burden countries, the largest scale-up of bedaquiline to date has been in South Africa.[103]

There are several reasons as to why more people have not been able to access these life-saving medicines. Due to limited data, recommendations for the use of bedaquiline and delamanid have been conservative. WHO guidelines recommend that MDR-TB be treated with at least four effective medicines. Bedaquiline and delamanid are recommended as "add-on" agents for people with MDR-TB who do not have other treatment options, and

for people at high risk for poor treatment outcomes (people with extensive TB disease and/or TB/HIV co-infection, and people who cannot tolerate other TB medicines). However, the uptake of bedaquiline and delamanid has been far lower than the actual need for these medicines.

In addition, there are important knowledge gaps on how best to use these newer TB medicines in treatment regimens. Notably, there is a lack of data on the combination of bedaquiline and delamanid; their interactions with other standard TB medicines and ARVs; and their safety and effectiveness in specific populations (such as pregnant women, children, and people living with HIV/AIDS). Optimal regimens and treatment duration are not known. In addition, bedaquiline and delamanid are not registered in many high-burden countries and are priced out of reach in many countries. Finally, implementation is seen as complex, due to the need for drug safety monitoring and reporting. All of these elements have led to an overall low uptake, and many people who would benefit from these medicines are missing out.

Bedaquiline and delamanid are available from GDF/Stop TB. GDF has delivered bedaquiline to the following countries featured in *Out of Step:* Armenia, Bangladesh, Belarus, Cambodia, DRC, Ethiopia, Georgia, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Myanmar, Nigeria, Pakistan, PNG, Philippines, Swaziland, Tajikistan and Viet Nam.

FINDINGS:

- Bedaquiline is included in the national guidelines for DR-TB treatment in 79% (23) of countries;
- Delamanid is included in the national guidelines for DR-TB treatment in 62% (18) of countries;
- In China, bedaquiline for adults is being piloted in 15 hospitals. In Viet Nam, bedaquiline is being used under research conditions (not for programmatic use) at three sites;
- In Afghanistan, current recommendations for delamanid use apply to adults (≥18yrs) with pulmonary MDR-TB, including people living with HIV. In South Africa, the clinical access programme for delamanid has been approved and has started in at least one site, with expansion to four more sites planned.

See table 8 for more information on the inclusion of bedaquiline and delamanid in national guidelines.

TABLE 8: NATIONAL GUIDELINES INCLUDE BEDAQUILINE AND DELAMANID

Bedaquiline included in national guidelines	Delamanid included in national guidelines
Afghanistan	Afghanistan
Armenia	Armenia
Bangladesh	Bangladesh
Belarus	Belarus
Cambodia	Cambodia
DRC	Georgia
Ethiopia	Kazakhstan
Georgia	Kenya
India	Kyrgyzstan
Indonesia	Mozambique
Kazakhstan	Myanmar
Kenya	Nigeria
Kyrgyzstan	Pakistan
Mozambique	PNG
Myanmar	Philippines
Nigeria	South Africa
Pakistan	Swaziland
PNG	Zimbabwe
Philippines	
Russian Federation	
South Africa	
Swaziland	
Zimbabwe	


Daro Sulakauri/MSF

KALE MANTKAVA, A DR-TB PATIENT, IN HIS HOSPITAL ROOM IN ABASTUMANI, GEORGIA.

SPOTLIGHT – MSF'S EXPERIENCE OF TREATING MDR-TB WITH BEDAQUILINE AND DELAMANID

Ongoing trials will yield more information on the best combinations and treatment duration for bedaquiline and delamanid. In the interim, MSF is working with national programmes to offer people optimal treatment (including bedaquiline and/or delamanid) adapted to their individual needs, with support from the endTB Medical Committee.

MSF is working with national treatment programmes in Armenia, Belarus, Georgia, India, Kenya, Kyrgyzstan, Mozambique, Myanmar, South Africa and Swaziland, giving people with MDR-TB and limited treatment options the best hope for a cure.

Results from cohorts of extremely difficult-to-treat patients without other treatment options have been impressive. In Armenia and Georgia, 82 people with MDR-TB received bedaquiline through compassionate use between April 2013 and April 2015. Most (84.2%) were resistant to FLQs, of which 48.8% were extensively drug-resistant. All had been treated with second-line drugs, while 39% had received clofazimine.[104]

Among the 64 people who were culture-positive at initiation, 54/64 (84.4%) achieved 6-month culture conversion (a sign that treatment is working). However, 10/54 (18.9%) reverted back to positive later in the treatment.Treatment outcomes were: 54.8% successful, 12.2% death, 7.3% failure and 21.9% lost to follow-up.[105]

These results show a very high rate of culture conversion for very resistant strains of MDR-TB. However, the high proportion of relapses after 6 months of treatment is alarming, calling into question WHO's previous recommendation of limiting bedaquiline to 24 weeks. In addition, the high proportion lost to follow-up – likely due to the long duration of treatment – remains a concern. Similar results were seen in a cohort of patients treated in Chechyna; a study comparing treatment with bedaquiline, linezolid and clofazimine to regimens without these medicines showed better culture conversion at 6 months.[105]

By the end of the first quarter of 2017:

- MSF had supported the use of bedaquiline and/or delamanid in more than 1,300 people with MDR-TB.
- 975 of them started bedaquiline-containing treatment (20 were under 18 years old).
- 342 of them (26 were under 18 years old) started delamanid-containing treatment.
- Using the endTB Medical Committee's criteria for the combination of bedaquiline and delamanid, 71 people with MDR-TB in nine countries, including Armenia, Belarus, India, Mozambique, South Africa and Swaziland, have received regimens containing both medicines.
- 294 people with MDR-TB have benefited from prolonged treatment with bedaquiline and/or delamanid beyond the standard 24 weeks.[106]

Short-course DR-TB regimen

In 2016, WHO issued a recommendation supporting a shorter RR- or MDR-TB treatment regimen (9 to 12 months versus up to 24 months) under specific criteria. The shorter regimen of existing medicines is only recommended for people with RR- or MDR-TB who have never received second-line TB medicines and who are not - or are highly unlikely to be - resistant to FLQs and SLIDs (based on second-line DST or, if unavailable, surveillance data on prevalence and types of drug resistance). In addition, WHO regrouped the medicines used for RR- and MDR-TB (see table 9, WHO: regrouped medicines recommended for RR- and MDR-TB).[99]

This recommendation was based on evidence from operational research studies, which found the shortened regimen to be more effective for eligible patients[99] – and the price dropped to less than US$ 1,000 per treatment course.[1] By 2016, shorter RR- and MDR-TB treatment was being successfully used in 23 African and Asian countries, with treatment success rates of 87% to 90%.[1]

Modelling the impact of shorter treatment on MDR-TB incidence found that shorter treatment has the potential to markedly reduce the incidence of MDR-TB if access to shorter and more effective treatment is expanded, and in the absence of additional drug resistance.[107]

FINDINGS:

- The WHO-recommended 9-month (shorter) MDR-TB treatment regimen is included in the guidelines in 45% (13) of countries. These countries include: Afghanistan, Bangladesh, Cambodia, CAR, DRC, Kyrgyzstan, Myanmar, PNG, Philippines, Swaziland, Tajikistan, Viet Nam and Zimbabwe;
- Four countries are recommending the same 9-month (shorter) MDR-TB regimen as recommended by WHO;
- According to national guidelines, five countries require a second-line DST by LPA before starting the short-term regimen.

SPOTLIGHT – SHORT-COURSE MDR-TB TREATMENT IN SWAZILAND

In January 2014, MSF and the Swaziland MoH piloted a short-course regimen to treat MDR-TB in 120 HIV-negative and HIV-positive adults and children; data from this study were among those used to inform the WHO short-course treatment guidelines. As of June 2016, 80 patients had finished treatment; overall 60 (75%) were cured, 10 (12%) died, 9 (11%) were not cured (underscoring the need for new TB medicines), and 1 person was lost to follow-up. The model of care enabled short-course treatment, but side effects remained problematic (30 people experienced severe adverse events).[108]

TABLE 9: WHO: REGROUPED MEDICINES RECOMMENDED FOR RR- AND MDR-TB[99]

GROUP A: Fluoroquinolones, in order of preference for use	levofloxacin, moxifloxacin, gatifloxacin
GROUP B: Second-line injectables	amikacin, capreomycin, kanamycin, streptomycin (in some cases)
GROUP C: Other core second-line agents, in order of preference for use	ethionamide/prothionamide, cycloserine/terizidone, linezolid, clofazimine
GROUP D: Add-on agents	**D1**: pyrazinamide, ethambutol, high-dose isoniazid
	D2: bedaquline, delamanid
	D3: p-aminosalicylic acid, Imipenem-cliastatin, (complementary) meropenem, amoxicillin-clavulanate, thioacetazone (only if HIV-negative)

JUSUP TAKES HIS MEDICINES FOR DRUG-SENSITIVE TB AT HIS LOCAL FAMILY MEDICAL CENTRE IN KYRGYZSTAN.

DR-TB treatment in children

Unfortunately, there are no child-friendly formulations to treat drug-resistant forms of TB. Data on the safety and effectiveness of bedaquiline and delamanid in paediatrics are limited. Based on data from an ongoing study in children, WHO has recommended that delamanid could be added to treatment for DR-TB in children and adolescents (6–17 years old) under specific circumstances (ineligibility for shorter treatment because of treatment history or resistance profile, or contraindications).[109]

Currently, bedaquiline is approved for adults ≥18 years old; an ongoing phase 2 study is exploring dosing, safety and efficacy of bedaquiline-containing TB treatment in ages 0-18,[110] and another in HIV-negative and HIV-positive infants, children and adolescents up to 18 years old is planned.

SPOTLIGHT – TREATING CHILDREN WITH NEWER DR-TB MEDICINES IN TAJIKISTAN

Dr Zulfiya Dusmatovam, an MSF medical doctor working with the MoH, explains the experience of using bedaquiline and/or delamanid with other drugs to treat children with DR-TB in Tajikistan. In 2015, 546 children were diagnosed with DR-TB, 21 with MDR-TB.

"A lot of precautions were taken at the beginning, when the first five paediatric patients were admitted for treatment with bedaquiline in 2015; they had to stay in the hospital for 6 months. Nowadays, both patients and doctors have more confidence in the drugs and patients are starting to receive treatment on an ambulatory basis, without hospitalisation. The good news is that the children tolerated the medication well and there was rapid sputum culture conversion [a sign that treatment is working]. For the first time, delamanid was used to treat children. No major side effects of the drug were reported and again, the five children who started taking this drug showed good tolerance of the medicines, and promising early results.

Paediatric fixed-dose combinations (FDCs) of DS-TB medicines have definitely made treatment easier for small children, since they don't have to swallow such a large number of pills every day. But there are currently no FDCs available for children with DR-TB, so in Tajikistan, MSF has supported the Ministry of Health with the introduction of drug-compounding techniques (in this case, the preparation of a syrup formulation) for some DR-TB drugs. The syrup formulation has certainly helped the youngest patients, who have difficulty swallowing tablets, and greatly improved both tolerability of, and adherence to treatment among children with DR-TB.

The Ministry of Health is updating its National Paediatric Tuberculosis guidelines, which will include use of the newer drugs – bedaquiline and delamanid – and drug-compounding techniques for children. This will encourage medical staff to scale up the use of new drugs in the country."

Management of co-infections

Collaborative TB and HIV activities are a key component of the End TB Strategy's Pillar 1.[48] Prevention, testing, care and treatment services for HIV and TB must be integrated and easily accessible to people living with, or at risk for, both infections.

TB and HIV are a deadly – and common – combination. People with weakened immune systems due to HIV or other causes, such as diabetes and malnutrition, are especially vulnerable to falling ill with and dying from TB.[111] At least one third of the world's 36.7 million HIV-positive people are co-infected with TB.[112] In 2015, only 55% of TB patients were tested for HIV.[1]

ART reduces the risk for and rate of TB among HIV-positive people,[113] and lowers TB-associated mortality among people living with HIV.[114] WHO now recommends ART for all HIV-positive people, initiated within 2 to 8 weeks of starting TB treatment (depending on CD4 cell count).[54]

People with diabetes are more susceptible to developing active TB; diabetes triples a person's risk of developing TB.[115] People with TB should be systematically screened for diabetes and vice versa (especially in settings with a high TB prevalence).[115]

HOW TB MEDICINES WORK

There are two types of TB organisms: some are actively reproducing and some are dormant (also known as persistors, or 'fat and lazy').[116] Most antibiotics can stop TB from reproducing. But to be effective, TB treatment must include medicines that can kill the dormant organisms - this is called 'sterilising activity'.[117,118] Getting rid of dormant TB organisms takes time, so treatment length is based on how quickly medicines can do this.[118]

Necessary set of medicines for the treatment of DR-TB: Countries must have access to all WHO-recommended DR-TB medicines, including repurposed medicines (amoxicillin-clavulanate, clofazimine, imipenem/cilastatin, levofloxacin, linezolid, meropenem, moxifloxacin). These medicines were developed and approved for use under other conditions, although they are active against and have improved outcomes for DR-TB. 'Companion drugs' are used to maintain the effectiveness of DR-TB treatment by preventing resistance to newer DR-TB medicines, such as bedaquiline and delamanid.

TB REGIMEN DEVELOPMENT

Since TB must be treated with combinations of medicines, the most effective research focuses on entire regimens and strategies to optimise them, instead of developing medicines one by one. The ultimate goal is to develop an affordable, short-course, oral 'pan-TB' regimen with few side effects.

3P: The 3P Project is dedicated to initiating a better, faster way to develop a short-course pan-TB regimen, instead of developing single medicines. The 3P Project has built affordability into drug development, because their costs are covered up front: prize money goes towards early-stage development, grants pay for trials that combine new medicines, an open collaborative platform ensures access for developers, and the pooling of data, intellectual property and products ensures accelerated and affordable access.

Several studies (including NC-005, NIX, TB PRACTECAL and endTB) are looking to increase effectiveness and shorten treatment duration by combining old, new and repurposed medicines with some promising TB medicines that are in the development pipeline, such as pretomanid – a medicine from the same family as delamanid - and sutezolid, which may be more tolerable than linezolid.[119]

MEDICINES: ACCESS AND AFFORDABILITY

Medicines need to be available and affordable to be effective. A conventional, WHO-recommended, standard 24-month treatment course for MDR-TB can cost between US$ 1,600 and US $ 4,000; this does not include clinical management, laboratory tests and hospitalisation, which can be up to 14 times higher than the price of the regimen. Currently, the price of delamanid in countries eligible for the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) is US$ 1,700 for a 6-month course.

Current pricing for a 6-month course of bedaquiline is US$ 900 in low- and middle-income countries (LMICs), US$ 3,000 in middle-income countries (MICs), US$ 30,000 in high-income countries (HICs), US$ 1,700 in Russian Federation and US$ 1,351 in other countries in the Commonwealth of Independent States (CIS) countries; or, otherwise available through a donation programme for GFATM eligible countries outside of CIS.[120]

WHAT NEEDS TO HAPPEN

Treatment gap: More effort is needed to close the deadly gap between adults and children who need treatment and those who are actually receiving it, for all forms of TB.

Co-infections: Co-infections should be managed effectively, especially TB/HIV co-infection.

Paediatric TB: Countries should introduce the updated paediatric FDCs as the standard of care for DS-TB.

Optimal DR-TB therapy:

- Steps should be taken to reduce the burden on people receiving treatment;
- Use of newer classes of TB medicines should be scaled up: in 2016, only 5% of people who could have benefited from treatment with bedaquiline or delamanid had access to these life-saving medicines;
- DR-TB regimens should be affordably priced and accessible to people who need them in all LMICs;
- As more data on new medicines become available, WHO should continue to update the guidance for introducing new medicines and update the WHO Model List of Essential Medicines (EML) with new and companion TB medicines; WHO should also adapt and conduct advanced DR-TB training on new medicines for technical advisors, NTPs, etc.

R&D: Governments should support the launch of innovative research to develop new, affordable all-oral regimens that are shorter, have fewer side effects and have a lower pill burden. This includes the 3P Project, designed to use innovative funding and pooling mechanisms to develop a 1-month cure for all forms of TB.

VELEMSENI MDLOVU, A DRUG-SENSITIVE TB PATIENT FROM NSALITJE IN SHISELWENI, SOUTH OF SWAZILAND.

Sami Siva

SEIKHOLIEN, AN MDR-TB PATIENT, SHOWS THE DAILY DOSE OF PILLS GIVEN TO HIM BY THE MSF STAFF NURSE IN MANIPUR, INDIA.

REGULATORY ENVIRONMENT FOR TB MEDICINES

KEY FINDINGS

- 75% (21/28) of countries have accelerated registration mechanisms in place that could potentially be applied to new and repurposed DR-TB medicines;
- Unregistered TB medicines are available through compassionate use or other national-level legal mechanisms in 89% (25/28) of countries;
- 41% (12) of countries are enrolled in the WHO Collaborative Registration Procedure;
- 28% (8/28) of countries have either bedaquiline or delamanid listed on their national Essential Medicines List (EML);
- Approximately half of the countries surveyed have more than 50% of the WHO-recommended medicines (Group A, B, C, D1, D2, D3) listed in their national EMLs (listed specifically in the anti-TB medicines category);
- Bedaquiline is registered in six countries and delamanid is not registered in any of the countries surveyed for this report;
- In 93% (26/28) of countries there is a policy in place that requires a prescription for TB medicines.

BACKGROUND

TB medicines should be quality-assured and WHO-prequalified (or approved by a stringent drug regulatory authority [SDRA]) to avoid falsified or counterfeit products.

Many important TB medicines have not been registered in high-burden countries, including TB medicines listed in the WHO EML. Furthermore, some of the necessary set of medicines for TB may not be registered for this use. Drug registration can be a lengthy process, given that national drug regulatory authorities (NDRAs) have their own procedures, timelines and capacities, and originator companies prioritise registering their drugs in the most profitable markets, instead of where they are needed the most. The WHO Collaborative Registration Procedure accelerates approval of and access to originator and generic medicines for public health needs in developing countries, including TB medicines. Using this procedure ensures that medicines can get to the people who need them faster.

Other mechanisms, such as import waivers or compassionate use programmes, can provide access to life-saving TB treatment in countries where the medicines are not registered.

National Essential Medicines List (EML)

The WHO Model List of Essential Medicines identifies medicines that are prioritised based on their safety, efficacy, cost-effectiveness and importance in meeting people's health needs. When a medicine is included in the EML, it sends a powerful signal to countries for their own national EML; this, in turn, can ease importation of the listed medicines.

The 20th edition of the EML includes most WHO-recommended TB medicines with a TB indication. Clofazimine, a key medicine of the MDR-TB shorter treatment regimen, has been added to the latest WHO EML as an anti-TB medicine.

> All TB medicines recommended in WHO guidelines should be included in WHO and national EMLs.

FINDINGS:

- Approximately half the countries surveyed have more than 50% of the medicines (Group A, B, C, D1, D2, D3) listed in their national EML (listed specifically in the anti-TB medicines category);
- No country has the full set of WHO-recommended DR-TB medicines under the TB section in their EML;
- In Georgia, no valid National EML exists currently, but one is in the process of being finalised and approved. In the interim, the WHO EML is being used as a reference. In Kyrgyzstan, the new national EML is currently being approved. Philippines is also in the process of updating its EML.

KEY REGULATORY POLICIES

COUNTRY	DR-TB medicines can receive accelerated registration	Unregistered TB medicines are available through CU/other legal mechanisms**	Country is enrolled in WHO Collaborative Registration Procedure
Afghanistan	No	Yes	No
Armenia	Yes	Yes	Yes
Bangladesh	Yes [a]	Yes	No
Belarus	No	Yes	No
Brazil	Yes	Yes	No
Cambodia	Yes	Yes	No
CAR	No	No	No
China	Yes	No	No
DRC	Yes	Yes	Yes
Ethiopia	Yes	Yes	Yes
Georgia	Yes [b]	Yes	Yes
India	Yes	Yes	No
Indonesia	Yes	Yes	No
Kazakhstan	Unknown	Unknown	No
Kenya	Yes	Yes	Yes
Kyrgyzstan	Yes	Yes	Yes
Mozambique	Yes	Yes	Yes
Myanmar	Yes	Yes	No
Nigeria	Yes	Yes	Yes
Pakistan	Yes	Yes	No
PNG	Yes	Yes	No
Philippines	No	Yes	Yes
Russian Fed.	No	Yes	No
South Africa	Yes	Yes	Yes
Swaziland	No [c]	Yes	No
Tajikistan	No	Yes	No
Ukraine	Yes	No	Yes
Viet Nam	Yes	Yes	No
Zimbabwe	Yes	Yes	Yes

LEGEND **Is this policy in place at the national level?** Yes · No · Unknown

(**) Compassionate use, expanded access programmes, import waivers or other legal mechanisms. **(a)** Only upon government declaring an emergency.**(b)** Only if already approved by an SDRA. **(c)** No medicines are registered in Swaziland, but as long as they are registered in South Africa, they can be used in Swaziland.

Quality assurance

TB medicines should be quality-assured – either WHO-prequalified or approved by an SDRA – to avoid substandard or falsified products. In 2011, WHO reported that 11% of certain first- and second-line TB medicines gathered from public TB treatment centres and private pharmacies in Armenia, Azerbaijan, Belarus, Kazakhstan and Ukraine failed quality standards, including 28% of rifampicin capsules.[121] A recent study of anti-TB medicines from private-sector pharmacies in 19 cities reported that 9% of all tested medicines were substandard; over 16% in 11 African countries, over 10% in India, and nearly 4% in Brazil, China, Russian Federation, Thailand and Turkey.[122]

Many NTPs use pooled procurement mechanisms for quality-assured TB medicines, such as through the GFATM. However, the GFATM has been changing its co-financing and allocation policies to fully or partially move out of MICs, including those with high burdens of TB and DR-TB. In the EECA region, home to 8 of the 16 MDR-TB high-burden countries, the GFATM's policies led to a 15% funding cut in the 2014–2016 allocation period; additional and significantly larger cuts are anticipated in the next allocation period (2017–2019). As EECA and other governments are rapidly forced to pay for a larger share of their TB medicines and diagnostics, they may transition from pooled procurement to national-led procurement. This could result in a lower quality of medicines being procured and also split the market for TB medicines and diagnostics between pooled procurement mechanisms and national procurement, which may have an impact on the pricing and quality of these commodities.

Early access provisions

Lack of registration can be a primary barrier to accessing medicines in high-burden countries, since some countries do not have mechanisms in place to provide access to unregistered medicines. Manufacturers may be reluctant to register their medicines in LMICs, even though these countries bear the brunt of the global TB epidemic. Some medicines that are used to treat DR-TB are registered for a different purpose (such as linezolid, clofazimine and imipenem/cilastatin) may also be unavailable.

Bedaquiline and delamanid have not been registered in many countries, and delamanid has not been registered in any high MDR-TB burden country. To offer a few examples from different parts of the world, neither drug has been registered in Kyrgyzstan, Myanmar or Mozambique, which have a high burden of MDR-TB; furthermore, clofazimine has not been registered with a TB indication, limiting the possibility to import it into these three countries. In Kyrgyzstan, MSF worked to provide access to these life-saving medicines by applying to the MoH Commission for import waivers, which are granted under certain conditions: for medicines that are on the National EML or included in the MoH treatment guidelines or protocols for first-line treatment.

FINDINGS:

- In South Africa, bedaquiline and linezolid can be accessed through national access mechanisms. Access to delamanid is only allowed through Otsuka's compassionate use programme with individual approval from the Medicines Control Council (MCC). Access to clofazimine is granted through an import waiver by the MCC on a named patient or group basis, and must be renewed every 6 months;

- According to national guidelines, 89% (25/28) of the countries surveyed for this report can procure unregistered TB medicines through compassionate use or other legal mechanisms. The countries where these mechanisms are not in place include CAR, China and Ukraine.

See table 10 for mechanisms across four countries.

TABLE 10: EXAMPLES OF MECHANISMS BEING UTILISED IN THE COUNTRIES SURVEYED

Country name	Mechanism being utilised
Ethiopia	Waiver
Georgia	Compassionate use, regular import procedure, exemption mechanisms, importation for unregistered medicines, under programmatic use
Tajikistan	Humanitarian access channel
Viet Nam	Research framework and Expanded Access Programme

Accelerated approval

Marketing authorisation can delay access to life-saving TB medicines, especially where the need for them is greatest. The pathways, requirements, local processes, timelines and capacity of NDRAs vary. A few countries lack NDRAs, while others do not always favour mutual recognition agreements or do not recognise technical assessments of SDRAs such as the European Medicines Agency (EMA) or the US Food and Drug Administration (USFDA).

In 2015, WHO launched the WHO Collaborative Registration Procedure to facilitate access to generic or originator medicines, including TB medicines, for public health needs in developing countries. Participating NDRAs have 90 days to review the dossiers of SDRA-approved or WHO-prequalified products, under confidentiality, in a globally harmonised format aligned with the same system used for WHO prequalification. Through this process, NDRAs can follow their national legislation and responsibilities, collect fees, and develop risk-management and pharmacovigilance plans with applicants.[123]

FINDINGS:

- 41% (12) of countries are enrolled in the WHO Collaborative Registration Procedure;
- The following countries do not have any legal mechanisms in place to allow for the accelerated registration of medicines, including DR-TB medicines: Afghanistan, Belarus, CAR, Philippines, Russian Federation, Swaziland and Tajikistan;
- Bedaquiline is registered in six countries (Armenia, China, India, Philippines, Russian Federation and South Africa), and delamanid is not registered in any of the countries surveyed for this report;
- 31% (9) of countries have all Group A medicines registered, 45% (13) of countries have all Group B medicines registered, 10% (3) of countries have all Group C medicines registered, 83% (24) of countries have all Group D1 medicines registered, no country has all Group D2 medicines registered and 10% (3) of countries have all Group D3 medicines registered.

See table 11 for registration status of bedaquiline and delamanid across surveyed countries.

TABLE 11: REGISTRATION OF BEDAQUILINE AND DELAMANID

Status	Bedaquiline	Delamanid
Registered	Armenia, China, India, Philippines, Russian Federation, South Africa	None of the surveyed countries have registered delamanid

BEDAQUILINE FOR TREATMENT OF MDR-TB AT THE NATIONAL CENTER FOR TUBERCULOSIS AND LUNG DISEASE, TBILISI, GEORGIA.

Prescription requirements

Too often, TB medicines are dispensed in the private sector without linkage to NTPs; people may seek treatment directly from a pharmacy, where staff are untrained, and necessary medicines may be unavailable or of poor quality. [124,125] Over-the-counter sales facilitate drug resistance, since people may not receive recommended, quality-assured medicines and/or regimens for their TB.[126] In 2014, WHO called for a ban on over-the-counter sales of TB medicines, and recommended a mixed public–private approach to ensure that providers who are not affiliated with NTPs are following international standards and national treatment guidelines.[126]

Although many countries have regulations prohibiting over-the-counter sales of TB medicines, these are difficult to enforce. WHO recommends making TB a notifiable disease, including tracking how all forms of TB are diagnosed and managed.[126]

FINDINGS:

- In 93% (26/28) of countries there is a policy in place that requires a prescription for TB medicines;
- Among the countries also surveyed for the 2015 *Out of Step* report, Brazil, Nigeria, Ukraine and Kyrgyzstan reported that a prescription is currently required (in 2017), whereas in 2015 they reported that a prescription was not required.

WHAT NEEDS TO HAPPEN

- **Quality:** Countries should ensure the procurement and use of quality-assured (including WHO-prequalified and SDRA-approved) TB medicines.
- **WHO prequalification:** Drug manufacturers of TB active pharmaceutical ingredients and finished products should pursue WHO prequalification.
- **Registration:** Drug companies must do better to prioritise the registration of medicines in countries with large numbers of people with TB, so that the medicines can be readily used; they should offer affordable prices to all LMICs.
- **TB indication:** Repurposed medicines, such as clofazimine, should have a TB indication and be registered with a TB indication in high-burden TB countries as a priority.
- **National mechanisms:** For their part, countries should provide mechanisms for the rapid entry of new medicines, including expedited registration through enrolment in the WHO Collaborative Registration Procedure or another mechanism, and the use of import waivers and other legal mechanisms until local registration is granted.
- **National EMLs:** Countries should revise their national EML according to the most recently updated WHO EML.
- **WHO:** WHO should provide support to countries in order to introduce compassionate use frameworks into their legal package and promote the Collaborative Registration Procedure.

PORTRAIT OF A CHILD IN INDONESIA

Stella Rajagukguk/Stop TB Partnership

PREVENTION

KEY FINDINGS

- Treatment for latent TB infection (LTBI), also known as preventive therapy, is provided to adult contacts, child contacts and people living with HIV in 14% (4) of countries; the policy is widely implemented in 75% (3/4) of them;
- Treatment for LTBI is provided to child contacts <5 years of age and people living with HIV in all countries surveyed; the policy is widely implemented in 52% (15) of them;
- Treatment for LTBI is provided to other at-risk populations beyond these two groups in 14% (4) of countries, which includes one or more categories recommended: prisoners, miners, people with silicosis, people with diabetes, and organ and transfusion recipients;
- In Afghanistan, Kenya and Swaziland, treatment for LTBI is provided to prisoners;
- A tuberculin skin test (TST) must be carried out prior to starting treatment for LTBI in 39% (11/28) of countries; the policy is being widely implemented in 45% (5/11) of them;
- 6-month isoniazid (INH) is provided as the preventive therapy regimen in all of the countries;
- 3–4 month isoniazid plus rifampicin is provided in three countries, and four countries provide a 3-month course of weekly rifapentine plus isoniazid (known as the 3HP regimen).

BACKGROUND

All persons exposed to TB are at risk of becoming sick. Globally, 30% of the population has LTBI.[1] Although they are infected with TB, they are not ill or infectious unless they develop active TB disease.[1] Over a lifetime, people with LTBI have a 5–10% risk of TB reactivation; this usually occurs within 5 years of infection. Preventive treatment reduces the risk of people with LTBI developing active TB by up to 90%.[1]

Prevention is essential to achieving the goals and targets of the End TB Strategy.[48] By 2025, the Strategy and the Global Plan to End TB calls for ≥90% coverage of two key initiatives as early as possible but not later than 2025: systematic screening for high-risk groups and those who have had close contact with people with infectious TB, and preventive therapy that protects people with LTBI from developing active TB disease.[3]

WHO recommends that all exposed persons in MICs and HICs that have a low TB burden (100 per 100,000 population) be offered LTBI treatment after exposure to TB. These guidelines will likely continue to evolve, because even this ambitious target overlooks a significant number of people who are also at risk in low-income countries LIC.

Treatment is more complex for people who have been exposed to drug-resistant forms of TB. Clinical assessments are required to look for active disease for prompt initiation of treatment. For those without active disease, there are currently two recommended strategies that may be followed: ongoing screening and monitoring for a minimum of 2 years, or provision of FLQ-based treatment of infection based on recent findings of a 90% reduction in TB incidence.[128] More clinical trials are underway.

Screening of household contacts and people living with HIV

Since TB is airborne, it can be easily transmitted in crowded places: households, prisons, hospitals, homeless shelters, cramped living quarters and workplaces, and even between minibus commuters.[129] Nearly 5% of those who have close contact with people with infectious TB have active TB disease, and over 50% of them have LTBI.[130] However, many people with early-stage TB do not exhibit the usual symptoms[131] and are unaware that they have TB.

Instead of relying on passive case finding (i.e., testing only those who seek health care for TB signs and symptoms), WHO recommends systematic screening of high-risk groups, with priority given to close contacts of people with TB and HIV-positive people, and workers exposed to silica; screening of other risk groups should be based on local epidemiology, resources, capacity and other factors.[48]

FINDINGS:

- All countries have policies in place to carry out active case finding for children under 5 years old who have been living in the same household as a confirmed TB patient. Half of these countries have widely implemented this policy;
- In 86% (25) of countries, there are policies in place to carry out active casefinding for all household contacts regardless of age, although only 44% (11/25) of these countries have widely implemented this policy;
- All countries have policies in place to conduct active casefinding among people living with HIV, and 66% (19) have widely implemented it. CAR is the only country for which the active casefinding policy for people living with HIV is unknown.

FUNDZILE MSIBI, MSF PSYCHOSOCIAL COORDINATOR, ENGAGES CHILDREN DURING AN HIV AND TB EDUCATION ROAD SHOW IN BUNYA, SWAZILAND.

Preventive treatment in children and people living with HIV/AIDS

WHO recommends prioritising those most vulnerable to developing severe and disseminated forms of TB, including children under 5 years old and people living with HIV/AIDS.

PEOPLE LIVING WITH HIV

The risk for TB reactivation is much higher for people living with HIV, who face an annual reactivation risk of 5% to 15%,[132] and TB is likely to be deadlier. Since 1998, WHO has recommended preventive therapy for all people living with HIV (without signs and symptoms of active TB).[133] Preventive therapy protects HIV-positive people from TB, even at high CD4 cell counts (>500 cells/μL), and especially when used in combination with ART.[55] However, countries have been slow to roll out preventive therapy (see table 12, Preventive therapy in countries surveyed (2015)). Worldwide, an estimated 37 million people were living with HIV/AIDS in 2015,[134] and 2.4 million of them were newly enrolled in care in 2015.[1] Only 910,000 (38%) started on preventive therapy.[1]

CHILD HOUSEHOLD CONTACTS

Globally, an estimated 1 million children under 15 years old developed TB in 2015;[135] it is estimated that half of them were under 5. TB is especially serious for children in this age group. Children are more vulnerable; TB is harder to diagnose in them and they are more likely to have serious forms of the disease, such as TB meningitis or disseminated TB; and the disease usually progress rapidly.[136]

In 2015, 1.2 million children under 5 years old were estimated to be household contacts of infectious TB patients and therefore eligible for preventive therapy; yet only 7.1% (or 87, 000) of them received it (see table 12, Preventive therapy in countries surveyed).[1]

PREVENTING MDR-TB

Treating household contacts of MDR-TB patients could help to prevent the spread of MDR-TB. By the time a person with MDR-TB is diagnosed, 5% to 10% of their household contacts have active TB and nearly 50% of them have LTBI.[130]

Preventive therapy for latent MDR-TB is challenging and relies on medicines that are likely to be effective, as DST can only be performed in people with active TB, and their contacts do not always have the same form of TB. Nonetheless, given the toxicity, limited effectiveness and expense of DR-TB treatment, it is critical to prevent progression of drug-resistant LTBI. Treatment of people who have been exposed to drug-resistant forms of TB is complicated, and relies on a detailed exposure history. All persons exposed to DR-TB should have urgent clinical assessments to look for active disease, so they can promptly be started on therapy based on the drug susceptibility pattern of the known source case.

In persons without active TB disease, two strategies may be followed: The first involves ongoing screening and monitoring for signs and symptoms of active

TB for a minimum of 2 years, with prompt initiation of empirical MDR-TB treatment based on the resistance pattern of the known contact for those with likely TB.[127] the second involves the provision of FLQ-based treatment of infection. A recent meta-analysis of the efficacy of FLQ-based treatment found a 90% reduction in TB incidence in persons exposed to DR-TB who received 6 months of FLQ-based therapy.[128] A trio of clinical trials are currently exploring optimal preventive regimens for MDR-TB contacts, using levofloxacin versus delamanid or placebo, but results are not expected until 2020.

TABLE 12. PREVENTIVE THERAPY IN COUNTRIES SURVEYED (2015)[1]

Country and classification	Coverage, by percent, of TB preventive therapy among HIV-positive people newly enrolled in care	Percentage coverage of preventive therapy for TB in estimated under-five children who were household contacts of lab confirmed TB
Bangladesh (■ ▲)	Not reported	22%
Cambodia (■)	25%	14%
Ethiopia (■ ● ▲)	47%	Not reported
Indonesia (■ ● ▲)	2%	Not reported
Kenya (■ ● ▲)	33%	5.5%
Mozambique (■ ● ▲)	45%	Not reported
Myanmar (■ ● ▲)	10%	3.6%
Nigeria (■ ● ▲)	20%	16%
Philippines (■ ▲)	43%	14%
South Africa (■ ● ▲)	38%	Not reported
Viet Nam (■ ▲)	Not reported	11%
Zimbabwe (■ ● ▲)	31%	31%

WHO classified high-burden countries: ■ TB, ● TB/HIV, ▲ MDR-TB

FINDINGS

- All countries are providing treatment for LTBI to children and people living with HIV/AIDS, while 52% (15) have widely implemented it;
- Swaziland, Russian Federation, Belarus and Brazil provide preventive therapy to adult contacts, child contacts and people living with HIV/AIDS. All four of these countries have widely implemented it, except for Swaziland, which is implementing the policy - but not on a wide scale;
- In 61% (17/28) of countries, it is not compulsory to carry out a test for LTBI, such as a TST or interferon-gamma releasing assay (IGRA), prior to prescribing preventive therapy but a clinical assessment is carried out to exclude active TB. Brazil and Kyrgyzstan request compulsory TSTs to select people eligible for preventive therapy, but when they have TST shortages – which occurs often – they prescribe preventive therapy based on a clinical evaluation;
- In all countries, the guidelines recommend 6-month isoniazid treatment to treat LTBI upon exclusion of active TB;
- In all countries, 6 months of daily INH is the preferred regimen. Some of the surveyed countries use different preventive therapies, as highlighted in table 13.

TABLE 13: EXAMPLES OF PREVENTIVE THERAPY REGIMENS IN THREE COUNTRIES THAT USE REGIMENS OTHER THAN INH ALONE

Country	Medicines used in preventive therapy and duration of treatment (including RPT, RIF and Rfb)
China	6 months INH, 3 months weekly RPT+INH
Georgia	6 months INH (preferred) 9 months INH 3 months on a weekly basis RPT+INH 3–4 months INH+RIF 3–4 months RIF
Russian Federation	6 months INH 3–4 months INH and RIF/Rfb 3 months (once a week) INH+RPT

INH = isoniazid, RIF = rifampicin, RPT = rifapentine, Rfb = rifabutin

SPOTLIGHT – LATENT TB AMONG CHILD CONTACTS IN ARMENIA

In Armenia, MSF followed 150 paediatric contacts of people with DR-TB for 24 months. The prevalence of LTBI among these children was high (52.7%), especially among those with smear-positive contacts. During follow-up, the incidence of LTBI was important (17 new infections/100 person-years); however, only two children had active TB disease at inclusion in the study (both were under 1 year old). These findings support TB screening and close follow-up for paediatric contacts, especially for infants and contacts of people with smear-positive TB, rather than preventive treatment in this setting.[137]

SPOTLIGHT – VILLAGE-BASED HEALTH WORKERS PROVIDE PREVENTIVE THERAPY TO CHILDREN IN ETHIOPIA

From 2012 to 2015, a TB REACH* project in Ethiopia focused on community-based active case finding, contact tracing, decentralised treatment and the provision of preventive therapy to children. The project used village-based health extension workers (HEWs) from Ethiopia's Health Extension Programme (HEP). The project was initiated in one zone (Sidama) of the Southern Region and was subsequently scaled up to eventually reach about 50% of the region's population.

Training and capacity-building was provided for general health workers and HEWs, who then conducted house-to-house visits as part of their routine activities in order to identify individuals with a cough for 2 or more weeks. HEWs collected sputum samples and prepared slides for smear microscopy. They then contacted supervisors to collect and transport the slides. Supervisors initiated treatment for people with smear-positive TB within the community, examined contacts and initiated preventive therapy for asymptomatic children. This approach resulted in a higher acceptability of and adherence to preventive therapy than in previous studies.

Although preventive therapy is recommended by the NTP, it had not been widely implemented until the HEW initiative was in place. Their outreach led to a doubling of people starting treatment and greatly improved treatment outcomes.

Of 1,693 asymptomatic children under 5 years old, 1,415 (84%) received preventive therapy. Treatment and follow-up of cases and preventive therapy were decentralised to the community, which improved uptake and adherence; very few people interrupted their preventive therapy.

A TB AND HIV OUTREACH EVENT ORGANISED BY MSF IN BHUNYA. MANZINI REGION, SWAZILAND.

WHAT NEEDS TO HAPPEN

- **Scale up screening and treatment for LTBI** particularly for people living with HIV, children or persons in close contact with people who have TB.
- **Reach key populations:** Countries need to develop programmes to reach vulnerable and key populations, including children, HIV-positive people, and prisoners, among other groups
- **Ensure that tests for TB infection are not mandatory for HIV-positive people, child contacts or persons with high-risk household exposures** prior to the initiation of LTBI treatment; HIV-positive people with negative symptom-based screening should be offered treatment for LTBI.
- **Scale up and optimise TB prevention for HIV-positive people:** All HIV-positive adults, adolescents and children should start ART, undergo routine screening for TB and be provided with treatment for latent or active TB.
- **Ensure that all persons exposed to DR-TB receive urgent assessments** to rule out active disease and are followed routinely over a period of 2 years.
- **Optimise treatment for LTBI** by making affordable FDCs and increasing the use of the 3HP regimen (3 months of weekly RPT + INH) for populations where effectiveness is clear.
- **Provide adherence support:** Countries need to ensure that people have the support they need to complete the full course of treatment for LTBI, and improve reporting of completion rates.
- **Monitor** access to and implementation of treatment for LTBI.
- **Research and development:** There is an urgent need for an effective preventive vaccine and better tools or biomarkers to identify groups among the 2 billion people with LTBI that are likely to progress to active TB and therefore, who could benefit from preventive therapy. Better, shorter preventive therapy regimens are needed, along with research on the most effective ways to deliver them.

A SLUM IN BANGLADESH.

The Global Fund to Fight AIDS, TB and Malaria

CONCLUSION

With the advent of improved TB diagnostic tests and medicines - and evidence of their efficacy in hand – we already have the means to conquer TB. Although more effective tests and treatments must be developed to improve the standard of care for TB, this task cannot deter governments and treatment providers from doing all they can do now to reduce TB deaths. The evidence cited in this report shows that many of the 1.8 million annual TB deaths could be averted if all affected countries fully implemented today's recommended policies and practices for TB prevention, diagnosis and treatment.

To accomplish this, countries must put TB at the top of their national health priorities. They must take the necessary steps to improve TB care in their own communities, and they must also advocate for additional funding, research and political attention on a global scale. Countries may need to revamp their drug regulatory pathways, adjust their procurement processes, update their TB guidelines and policies, accelerate full implementation of these policies, and ensure health budgets are matched to health needs. A multi-sector approach at the national and international level is required.

None of this will be easy, but we cannot afford the alternative: Failure to fully scale up each step towards successful TB treatment will hasten the spread of drug-resistant forms of the disease and prolong the dismal trends in missed diagnoses, long-term morbidity and avoidable TB deaths.

Ending TB requires the implementation of broad-based public health measures and thoughtful design of patient-centred models of care. For example, scaling up access to rapid testing to identify DR-TB is essential, but not sufficient. A single test cannot make TB treatment more tolerable, shorter or more effective. Once diagnosed, people need access to the best treatments available, along with education, counselling and support to help them successfully complete their treatment. Effective TB diagnosis and treatment must be made affordable for national programmes, so they can provide care to all who need it. In 2016, only 5% of people who could benefit from the newer TB medicines bedaquiline and delamanid had access to these life-saving medicines; these treatments must be made available to all people who need them. Development of new TB treatments must be centred on meeting people's health needs by prioritising affordability and access early in the research process, and by focusing on the development of treatments that are easy for patients to tolerate and complete and that can cure all forms of TB disease.

We have the means to end the global TB epidemic. We have the strategies, tools, plans and targets to guide our way. What we need now is political will, adequate resources, accelerated research, and full implementation of the policies and practices that we know will reduce TB suffering and death.

NEEDED: 10 COMMITMENTS FOR TB

Governments must re-commit to fighting TB, with urgency, so that the Global Plan to End TB milestones are met. By 2020, the milestones to be achieved include: increasing treatment coverage to over 90%, reducing TB incidence by 20% (compared to 2015) and reducing mortality by 35% (compared to 2015). Governments should commit to a set of time-bound targets at the Global TB Ministerial Conference in Moscow in November 2017 and UN High-Level Meeting on TB in 2018, as well as taking other opportunities to do so. Examples include:

- **Implement the latest WHO TB prevention, testing, and treatment guidelines by 2018.**
- **Diagnose people who develop TB (estimated at over 10 million every year).**
- **Increase the coverage and capacity to properly and promptly deliver optimal LTBI treatment.**
- **Improve DR-TB cure rates through appropriate use of newer classes of medicines and shorter regimens and by providing decentralised, patient-centred treatment, including ambulatory care.**
- **Find and treat all children with TB, including children exposed to TB.**
- **Implement 'test and start' immediate ART to people living with HIV.**
- **Fund TB programmes and the rollout of innovations needed to improve testing and treatment; the accelerated scenario requires doubling the amount of funding currently available per year, to US$ 12 billion per year.**
- **Fund R&D and ensure biomedical innovation benefits all. An additional US$ 1.17 billion per year is needed by 2018 from G20 countries.[138] Initiatives such as the 3P project (with its goal of a 1-month cure for all forms of TB) that designate the products of research as global public goods should be supported to ensure that the products they produce are affordable and accessible to all.**
- **Leave no one behind by eliminating catastrophic costs associated with TB and providing adequate and appropriate services to key populations, including prisoners, refugees, detainees, health care workers, people who use drugs and alcohol and persons with co-morbidities including HIV.**
- **End TB discrimination, and forcible incarceration and forced deportation of migrants simply because they have TB.**

THE GLOBAL PLAN TO END TB

The Global Plan to End TB 2016–2020 is a costed plan for implementing the first 5 years of the End TB Strategy, moving from the slow decline in TB incidence and mortality towards "bending the curves" – reducing incidence and mortality by 20% and 35%, respectively.

The Global Plan proposes that governments include plans to achieve three people-centred 90-(90)-90 targets, providing appropriate treatment to at least 90% of people with all forms of TB, including 90% of people from key and vulnerable populations. These targets address the unacceptable gaps in care experienced by people who are ill with TB.

The Stop TB Partnership will measure and report on progress towards meeting the 90-(90)-90 targets. The first report will be launched in 2017; it will establish baselines for national and global responses to TB, drawing on national TB data from WHO and additional information from NTPs, the European Centre of Disease Prevention and Control (ECDC), and regional and local projects working with key populations, among others. Reports will be launched annually from 2016–2020 to mark the 5-year roadmap towards ending the global TB epidemic by 2030.

FILL THE TB FUNDING GAP

The Global Plan to End TB 2016–2020 includes a costed blueprint for reaching the 2020 End TB Strategy milestones. Over a 5-year period, a total of US$ 56–58 billion is needed to implement TB programmes worldwide.[3]

In 2015, funding available for TB prevention, diagnosis and treatment was US$ 6 billion.[1] The Global Plan stated that the funding required for 2016 was US$ 9.9 billion, and US$ 12 billion is required for 2017. The available funding for TB prevention, diagnosis and treatment needs to double by 2017 from the 2015 levels.[3]

A further US$ 9 billion is needed over the 2016–2020 time period to fund R&D for new tools, including vaccines, drug regimens and diagnostic tests.[3] The available funding for R&D needs to almost triple to meet this need. However, it is of great concern that 2015 funding for TB R&D fell to its lowest level since 2008. [139]

NISCHAYA, AN XDR-TB PATIENT, AT HOME IN THE AMBEDKAR NAGAR AREA OF MUMBAI, INDIA.

ABBREVIATIONS

ACD1 – Ambulatory care day 1
ART – Antiretroviral therapy
CIS – Commonwealth of Independent States
DR-TB – Drug-resistant tuberculosis
DS-TB – Drug-sensitive tuberculosis
EECA – Eastern Europe Central Asia
EMA – European Medicines Agency
EML – Essential Medicines List
FDC – Fixed-dose combination
GFATM – Global Fund to Fight AIDS, Tuberculosis and Malaria
GLI – Global Laboratory Initiative
HIC – High-income country
HIV – Human immunodeficiency virus
IGRA – Interferon Gamma Release Assay
IPT – Isoniazid preventive therapy
LAM – Lateral flow urine lipoarabinomannan
LIC – Low-income country
LMIC – Lower middle-income country
LPA – Line probe assay
LTBI – Latent TB infection
MDR-TB – Multidrug-resistant tuberculosis
MIC – Middle-income country
MSF – Médecins Sans Frontières
MTB – Mycobacterium tuberculosis
NDRA – National drug regulatory authority
NGO – Nongovernmental organisation
PLWHA – People living with HIV/AIDS
POC – Point of care
PQ – Prequalification
R&D – Research and development
RR-TB – Rifampicin-resistant tuberculosis
SDRA – Stringent Drug Regulatory Authority
SDGs – Sustainable Development Goals
SEA – South-East Asian
SSA – Sub-Saharan African
TB – Tuberculosis
USFDA – US Food and Drug Administration
WHO – World Health Organization
XDR-TB – Extensively drug-resistant tuberculosis

GLOSSARY

Active case finding: Strategy of actively screening and diagnosing individuals at high risk for TB (e.g., people living with HIV, miners, etc.). Risk groups vary, depending on national TB epidemiology.

ART: Antiretroviral therapy (ART) is used to treat HIV. The standard of care is a combination of medicines that target different steps in the virus lifecycle to prevent it from replicating and to prevent the development of drug resistance. ART dramatically reduces mortality and morbidity rates among HIV-positive people, and improves their quality of life.

Category II (Category 2) treatment: A TB treatment strategy that is no longer recommended

CD4 count: Testing done in people who are HIV-positive to measure the number of CD4 T-cells in a sample of blood; this number indicates the status of a person's immune system.

Clinical trials: Studies looking at medical strategies, treatments and devices to see if they are safe and effective in people.

Compassionate use: The terms "compassionate use," "expanded access" or "special access" refer to programmes that are intended to provide potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or to 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 medicine 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 at high risk of having contracted TB due to close contact with an individual who has infectious TB.[126]

Culture: Bacterial culture is a laboratory method that multiplies bacteria to see if they are present in a sample from a patient. Culturing lets bacteria grow in a predetermined culture medium under controlled laboratory conditions outside of the natural environment where the bacteria usually grow (e.g., for TB, the human body).

Culture-converted: A person whose last two clinical samples no longer show growing *M. tuberculosis*, implying that the bacteria are no longer present – a sign that TB treatment is working.

Drug resistance: When a drug used to treat an illness, including TB, is ineffective; it does not kill viruses or bacteria, or prevent them from growing. When a drug is not effective against a strain of *M. tuberculosis*, the bacteria are said to be drug-resistant. Bacteria can be resistant to one or more drugs.

Drug-susceptible/drug-sensitive TB: When a given drug is effective (meaning it kills bacteria or prevents it from reproducing) against a type of virus or bacteria. This means that the drug can help to clear infections (although TB and many other infections need to be treated with more than one drug). TB strains that are sensitive to all first-line drugs are called drug-susceptible or drug-sensitive.

Drug-resistant TB (DR-TB): A broad term to encompass all forms of drug-resistant TB, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB.

Essential Medicines List: A list of the minimum medicine needs for a basic health care system. The EML includes the most effective, safe and cost-effective medicines for priority conditions. WHO updates its EML every 2 years. The WHO EML serves as a model for national EMLs.

Extensively drug-resistant TB: see XDR-TB

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 first drugs used 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-sensitive TB.

Fixed-dose combination (FDC): A combination of more than one medicine in a single tablet.

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 these three diseases through treatment and care programmes. It channels 82% of the international financing for TB.

Group 5 TB medicines: Anti-TB medicines with unclear efficacy or an unclear role in MDR-TB treatment as per WHO MDR-TB guidelines.

High TB burden countries: As defined by WHO, the 30 high TB burden countries are the 20 countries with the highest estimated number of incident TB cases

plus the top 10 countries with the highest estimated TB incidence rate that are not in the top 20, by absolute number (threshold: >10 000 estimated incident TB cases per year).

High MDR-TB burden countries: As defined by WHO, the 30 high MDR-TB burden countries are the 20 countries with the highest estimated numbers of incident MDR-TB cases plus the top 10 countries with the highest estimated MDR-TB incidence rate that are not in the top 20, by absolute number (threshold: >1000 estimated incident MDR-TB cases per year).

Microscopy: Currently the most commonly used TB diagnostic test, using two or three samples per person. 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.

Multidrug-resistant TB (MDR-TB): MDR-TB is resistant to at least two TB medicines, including isoniazid and rifampicin, the two most powerful first-line antibiotics used for TB treatment.

Mycobacteria: Types of bacteria of the genus *Mycobacterium* that cause disease, including 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; it was first discovered in 1882 by Robert Koch.

Point-of-care (POC) testing: When diagnosis is carried out as close as possible to where patient care is provided. The driving notion behind point-of-care testing is for the test to be as convenient as possible and give immediate results, leading to the prompt initiation of treatment.

Preventive therapy: Preventive treatment, also known as chemoprophylaxis, to reduce the risk of (i) a first episode of TB occurring in people exposed to infection or with latent infection and (ii) a recurrent episode of TB.

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

Repurposed drugs: Drugs that were not developed against TB, but are effective and used to treat some forms of DR-TB.

Second-line drugs: Second-line drugs are used in people who have forms of TB that are resistant to first-line drugs. Second-line TB drugs are less effective than first-line drugs and have more side effects.

Second-line DST: Testing for resistance to second-line injectable TB drugs and fluoroquinolones.

Smear-positive pulmonary TB: An individual whose sputum is positive for acid-fast bacilli (AFB) by smear microscopy.

Smear-negative pulmonary TB: An individual whose sputum is negative for AFB by smear microscopy, but is diagnosed as TB based on other methods such as culture.

Stringent regulatory authority (SDRA): An SDRA is defined as an International Committee on Harmonization (ICH) member country, an ICH observer or any country whose regulatory authority is associated with an ICH member through a legally binding mutual recognition agreement, or is approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Art. 58 of European Union Regulation (EC9 No. 726/2004) or United States FDA tentative approval.

Task shifting: The rational redistribution of tasks among teams of health care workers. Specific tasks are moved, where appropriate, from highly qualified health care workers to health care workers with less training and fewer qualifications in order to increase efficiency.

TB REACH: TB REACH is a multi-lateral funding mechanism primarily supported by Global Affairs Canada, with additional funding from Bill & Melinda Gates Foundation. The Indonesia Health Fund has also made a pledge to support TB REACH's Indonesian effort. TB REACH provides grants to partners for testing innovative approaches and technologies aimed at increasing the number of people diagnosed and treated for TB, decreasing the time to appropriate treatment and improving treatment success rates. It combines fast-track, results-based financing and rigorous, external monitoring and evaluation (M&E) to produce results, so other donor agencies and/or national governments can scale up successful approaches and maximise their own investments.

Universal DST: Providing drug-sensitivity testing (DST) for at least rifampicin in all patients with bacteriologically confirmed TB, and providing additional DST for at least fluoroquinolones and second-line injectable agents for all people who have rifampicin-resistant TB.

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 TB. Please consult http://apps.who.int/prequal/.

WHO 'test and start' recommendation: A recommendation that all HIV-positve receive ART, regardless of CD4 cell count.

XDR-TB (extensively drug-resistant TB): Patients are described as suffering from 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.

I. DIAGNOSIS

DIAGNOSIS: ACCORDING TO NATIONAL POLICY	Xpert MTB/RIF is the initial TB diagnostic test for adults and children being investigated for TB	Xpert MTB/RIF is the initial TB diagnostic test for high-risk groups*	TB-LAM is used to diagnose TB in PLWHA with CD4 ≤ 100 µL or seriously ill	DST for rifampicin is done for all bacteriologically-confirmed TB cases	First-line DST (rifampicin and isoniazid) is done for all RR-TB cases or for people at risk of DR-TB
Afghanistan	●	○	●	●	●
Armenia	● [a]	● [a]	●	●	●
Bangladesh	●	●	●	●	●
Belarus	● [b]	● [b]	●	●	●
Brazil	●	●	●	●	●
Cambodia	●	●	●	○	●
CAR	●	○	⊗	●	○
China	●	●	●	○	●
DRC	●	○	●	●	●
Ethiopia	●	●	●	●	●
Georgia	●	●	●	●	●
India	●	○	●	●	○
Indonesia	○	○	●	?	?
Kazakhstan	●	●	●	●	●
Kenya	○	○	●	○	●
Kyrgyzstan	○ [d]	○	●	○	○
Mozambique	○	○	●	○	○
Myanmar	●	●	●	● [f]	○ [f]
Nigeria	○	●	●	○	●
Pakistan	●	○	●	○	●
PNG	○	○	●	○	○
Philippines	●	○	●	●	○
Russian Fed.	○ [g]	○ [g]	●	●	●
South Africa	●	●	●	●	●
Swaziland	●	●	●	●	●
Tajikistan	○	○	●	○	○
Ukraine	●	●	●	●	●
Viet Nam	●	●	●	●	●
Zimbabwe	●	●	⊗	●	●

DIAGNOSIS: ACCORDING TO NATIONAL POLICY	Second-line DST (fluoroquinolones and second-line injectable agents) is done for at least all RR-TB cases	LPA is the initial test for second-line DST**	Active case finding for TB is carried out among PLWHA	Active case finding for TB is carried out for household contacts under the age of 5	Active case finding for TB is carried out for all household contacts
Afghanistan	●	●	?	?	?
Armenia	●	●	●	●	●
Bangladesh	●	?	?	?	●
Belarus	●	?	●	●	●
Brazil	●	●	●	●	●
Cambodia	● [c]	?	●	●	●
CAR	?	●	●	●	●
China	●	●	●	●	●
DRC	● [c]	●	●	●	●
Ethiopia	●	●	●	●	●
Georgia	●	●	●	●	●
India	●	●	●	●	●
Indonesia	●	?	?	●	●
Kazakhstan	●	●	●	●	●
Kenya	●	●	●	●	●
Kyrgyzstan	●	●	●	●	●
Mozambique	● [e]	●	●	●	●
Myanmar	● [f]	●	●	●	●
Nigeria	✕	●	●	●	●
Pakistan	?	?	?	?	?
PNG	●	?	●	●	●
Philippines	●	●	●	●	●
Russian Fed.	●	●	●	●	●
South Africa	●	●	●	?	?
Swaziland	●	●	●	●	●
Tajikistan	●	●	●	●	●
Ukraine	●	●	●	●	●
Viet Nam	●	●	●	●	●
Zimbabwe	●	●	●	●	●

LEGEND

Is this policy in place at the national level? Yes ● No ● Unknown ?

If Yes, is the policy being implemented? Yes ● No ● Unknown ? Yes, but not widely ● No ✕ Unknown ?

(*) High-risk groups include adults and children at risk for drug-resistant TB and HIV-associated TB. **(**)** Drug-sensitivity testing to fluoroquinolones and second-line injectables for patients with confirmed RR- or MDR-TB. **(a)** The initial diagnostic test is microscopy but regardless of microscopy result, every person to be evaluated for TB is tested with Xpert. **(b)** Part of an initial diagnostic package of tests. **(c)** Only select groups of patients are eligible. **(d)** At facilities that offer DR-TB regimens with BDQ or DLM. **(e)** No, but second-line DST is available at National Reference Lab. **(f)** Implementation of the 2017 guidelines is expected for the second half of 2017. **(g)** Xpert is part of a package of diagnostic tools; other diagnostic tests can be used, including other rapid molecular methods.

II. MODELS OF CARE

MODELS OF CARE: ACCORDING TO NATIONAL POLICY	DS-TB treatment is started at the primary health care level*	DR-TB treatment is started at the district level*	Nurses and health workers other than doctors can start adults on DS-TB treatment	Hospitalisation is NOT required for DS-TB treatment*,◆	Hospitalisation is NOT required for DR-TB treatment*,◆
Afghanistan	●	●	●	●	●
Armenia	● [a]	● [a]	● [a]	●	● [a]
Bangladesh	●	○	○	●	●
Belarus	●	●	●	● [a]	● [a]
Brazil	●	●	●	●	●
Cambodia	●	●	●	●	●
CAR	●	●	●	●	●
China	●	●	●	●	●
DRC	●	●	●	●	●
Ethiopia	●	●	●	●	●
Georgia	● [b]	● [a]	●	●	●
India	●	●	●	●	●
Indonesia	?	?	●	●	●
Kazakhstan	●	●	●	●	●
Kenya	●	●	●	●	●
Kyrgyzstan	○	●	●	●	●
Mozambique	●	○	●	●	●
Myanmar	●	○	●	●	●
Nigeria	●	●	●	●	●
Pakistan	?	●	●	●	●
PNG	●	●	●	●	●
Philippines	●	○	●	●	●
Russian Fed.	●	● [c]	●	●	●
South Africa	●	?	●	●	●
Swaziland	●	●	●	●	●
Tajikistan	○	○	●	●	●
Ukraine	●	✕	●	●	●
Viet Nam	●	●	●	●	●
Zimbabwe	●	●	●	●	●

MODELS OF CARE: ACCORDING TO NATIONAL POLICY	TB treatment is started in facilities providing HIV care	HIV treatment is started in facilities providing TB care	The same health workers provide TB and HIV treatment at primary health care level	ARV treatment is offered to all PLWHA ('test and start')	If NO, the CD4 count (cells/μL) threshold for ART initiation is...
Afghanistan	?		●	●	≤ 350
Armenia	●	●	●	●	≤ 500
Bangladesh	●	●	●	●	≤ 500
Belarus	●	●	●	●	≤ 350
Brazil	●	●	●	●	
Cambodia	●	●	●	⊗	
CAR	●	●	●	●	≤ 500
China	●	●	●	●	
DRC	●	●		●	
Ethiopia	●	●	●	●	
Georgia	●	●	●	●	
India	●	●	●	●	≤ 500
Indonesia	●	●		●	≤ 350
Kazakhstan	●	●	●	●	≤ 350
Kenya	●	●	●	●	
Kyrgyzstan		●	●	●	≤ 500
Mozambique	?	●	●		
Myanmar	?	●	●	●	≤ 500
Nigeria	●			●	≤ 500
Pakistan	●	●	●	●	≤ 500
PNG			●	●	
Philippines				●	≤ 200
Russian Fed.	●	●	●	●	≤ 500
South Africa	●	●	●		
Swaziland	●	●		●	
Tajikistan	●	●		●	≤ 350
Ukraine	●		●	●	≤ 500
Viet Nam		?	?	● [d]	≤ 500
Zimbabwe	●	●	●	●	≤ 500

LEGEND

Is this policy in place at the national level? ● Yes ● No ? Unknown

If Yes, is the policy being implemented? ● Yes ● Yes, but not widely ⊗ No ? Unknown

(*) Including smear-positive individuals. In some countries exceptions are made for people who are smear-negative and on a case by case basis. **(◆)** The implementation of the policy was not assessed for the hospitalisation questions. **(a)** Except for people who are smear-negative and on a case by case basis. **(b)** Patient receives a prescription at TB facilities. **(c)** DR-TB treatment can be started and dispensed from the district level, but only after decision and prescription from the regional TB committee. **(d)** Test and start in mountainous, coastal and remote provinces.

III. TB & DR-TB TREATMENT

TB & DR-TB TREATMENT: ACCORDING TO NATIONAL POLICY	Guidelines for children reflect the latest WHO guidance	Increased doses of first-line drugs for children are in line with latest WHO guidance**	New paediatric TB FDCs are the standard of care	DR-TB treatment reflects the latest WHO guidelines	Reflect WHO guidance on bedaquiline use for adults	Reflect WHO guidance on delamanid use for adults and children	Includes the WHO-recommended, 9-month (shorter) MDR-TB treatment regimen
Afghanistan	●	●	?	?	✕	✕	?
Armenia	●	●	●	○	●	●	●
Bangladesh	?	?	?	?	?	?	○
Belarus	●	●	●	●	●	●	●
Brazil	●	●	●	●	●	●	●
Cambodia	●	?	?	●	?	?	?
CAR	●	●	○	●	●	●	○
China	●	●	●	○	●	●	●
DRC	●	●	●	●	○	●	○
Ethiopia	●	●	✕	?	●	●	● [a]
Georgia	●	●	●	●	●	✕	●
India	○	●	✕	●	○	●	●
Indonesia	?	?	●	?	?	●	●
Kazakhstan	● [*]	●	●	?	?	?	●
Kenya	●	●	○	●	○	○	●
Kyrgyzstan	?	?	?	○	○	✕	○
Mozambique	?	?	?	○	○	○	● [b]
Myanmar	✕	●	✕	●	●	●	○
Nigeria	●	●	●	●	●	○	●
Pakistan	●	●	● [*]	?	?	?	●
PNG	●	●	○	●	○	○	○
Philippines	● [c]	●	●	●	○	○	?
Russian Fed.	●	●	●	?	●	●	●
South Africa	○	?	●	○	○	○	● [d]
Swaziland	✕	✕	●	●	●	●	○
Tajikistan	●	●	●	●	● [e]	● [e]	○
Ukraine	●	◯	●	? [f]	●	●	●
Viet Nam	●	●	●	?	●	●	○
Zimbabwe	●	●	●	●	○	○	✕

TB & DR-TB TREATMENT: ACCORDING TO NATIONAL POLICY	Details of 9-month (shorter) treatment regimen	Second-line DST by LPA (e.g. Hain) should be performed before starting 9-month treatment course
Afghanistan	4-6 Mfx-Km-Pto-Cfz-Z-E-$H_{high-dose}$-VB6 / 5 Mfx-Cfz-Z-E-VB6	?
Armenia	◯	◯
Bangladesh	4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\ dose}$-E / 5 Mfx-Cfz-Z-E	?
Belarus	◯	◯
Brazil	◯	◯
Cambodia	4-6 Km-Mfx-Eto-Cfz-$H_{high-dose}$-E-Z / 5 Mfx-Cfz-E-Z	?
CAR	4 Km-Mfx-Pto-Cfz-E-Z-$H_{high-dose}$ / 5 Mfx-Cfz-E-Z	
China	◯	◯
DRC	4-Km-Mfx-Pto-$H_{high-dose}$-Cz-E-Z / 5 Mfx-Cfz-E-Z (or 5 Mfx-Pto-Cfz-$H_{high-dose}$-Z-E)	
Ethiopia	◯	◯
Georgia	◯	◯
India	◯	◯
Indonesia	◯	◯
Kazakhstan	◯	◯
Kenya	◯	◯
Kyrgyzstan	4-6 Cm(Km)-Mfx-Cfz-Z-E-$H_{high-dose}$-Pto / 5 Mfx-Cfz-E-Z-Pto	
Mozambique	◯	◯
Myanmar	?	?
Nigeria	◯	◯
Pakistan	◯	◯
PNG	6 Km-Mfx- Pto-Cfz-Z-$H_{high-dose}$-E/5 Mfx-Cfz-Z-E	
Philippines	4-6 Mfx-Km-Pto-Cfz-Z-E-$H_{high-dose}$ / 5 Mfx-Cfz-Z-E	
Russian Fed.	◯	◯
South Africa	◯	◯
Swaziland	4-7 Km-$Mfx_{high-dose}$-Pto-Cfz-$H_{high\ dose}$-E-Z / 5 $Mfx_{high-dose}$-Pto-Cfz-E-Z)	
Tajikistan	4-6 Cm (Am)-Mfx-Pto-Cfz-Z-$H_{high-dose}$-E / Mfx-Cfz-Z-E-Pto	?
Ukraine	◯	◯
Viet Nam	4-6 Km-Lfx-Cfz-Pto-$H_{high-dose}$-E-Z / 5 Lfx-Cfz-E-Z	
Zimbabwe	4-6 Km-Mfx-Cfz-Z-E-$H_{high-dose}$-Eto / 5 Mfx-Z-Cfz-E	

LEGEND

Is this policy in place at the national level? Yes · No · Not applicable · Unknown

If Yes, is the policy being implemented? Yes · Yes, but not widely · No · Unknown

(*) The data could not be verified. **(**)** Isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/ day rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/ day pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg) ethambutol (E) 20 mg/kg (range 15–25 mg/kg). **(a)** Will be included in the new paediatric guidelines **(b)** New DR-TB guidelines in development include shorter MDR-TB regimens per WHO criteria and the NTP plans to enroll the first patients in July 2017. **(c)** New guidelines in development include paediatric FDCs. **(d)** New DR-TB guidelines in development include shorter MDR-TB regimens. **(e)** Implementation in pilot sites. **(f)** Guidelines need to be updated to reflect the latest groupings, including the specific mention of new and repurposed drugs.

IV. REGULATORY ENVIRONMENT FOR TB MEDICINES

REGULATORY ENVIRONMENT FOR TB MEDICINES: ACCORDING TO NATIONAL POLICY	DR-TB medicines can receive accelerated registration	Group A medicines are registered*	Group B medicines are registered*	Group C medicines are registered*
Afghanistan	🔴	Yes, except for Gfx	Yes, except for Km	Yes
Armenia	🟢	Yes, except for Gfx	Yes	Yes, except for Eto and Pto, Cfz
Bangladesh	🟢 [a]	Yes, except for Gfx	Yes, except for Cm, Km	Yes, except for Eto and Pto, Cs and Trd
Belarus	🔴	Yes, except for Gfx	Yes, except for S	Yes, except for Cfz
Brazil	🟢	Yes	Yes, except for Km	Yes, except for Cfz
Cambodia	🟢	Yes [i]	Yes [i]	Yes (Lzd unknown) [i]
CAR	🔴	Unknown	Unknown	Unknown
China	🟢	Yes	Yes	Yes, except for Eto and Pto
DRC	🟢	Unknown [ii]	Unknown [ii]	Unknown [ii]
Ethiopia	🟢	Yes, except for Gfx	Yes, except for S	Yes, except for Cs and Trd, Lnz, Cfz
Georgia	🟢 [b]	Yes, except for Gfx	Yes	Yes, except for Eto and Pto, Cs and Trd, Cfz
India	🟢	Yes	Yes	Yes
Indonesia	🟢	Yes, except for Gfx	Yes, except for Cm	No
Kazakhstan	?	Yes, except for Gfx [i]	Yes [i]	Yes, except for Lzd, Cfz [i]
Kenya	🟢	Yes	Yes	Yes
Kyrgyzstan	🟢	Yes, except for Gfx	Yes	Yes, except for Eto and Pto, Cs and Trd, Cfz
Mozambique	🟢	Yes, except for Gfx	Yes	Yes, except for Cfz
Myanmar	🟢	Yes, except for Gfx	Yes, except for Am, Cm	Yes, except for Eto and Pto, Cfz
Nigeria	🟢	Yes	Yes, except for Cm, Km	No
Pakistan	🟢	Yes	Yes	Yes, except for Cfz
PNG	🟢	NA [iii]	NA [iii]	NA [iii]
Philippines	🔴	Yes, except for Gfx	Yes, except for Cm, Km	Yes, except for Cfz
Russian Fed.	🔴	Yes	Yes	Yes, except for Cfz
South Africa	🟢	Yes	Yes	Yes, except for Cfz
Swaziland	🔴 [c]	No [iv]	No [iv]	No [iv]
Tajikistan	🔴	Yes, except for Gfx	Yes, except for Cm	Yes, except for Eto and Pto, Cs and Trd, Cfz
Ukraine	🟢	Yes, except for Gfx	Yes	Yes, except for Cfz
Viet Nam	🟢	NA [v]	NA [v]	NA [v]
Zimbabwe	🟢	Yes, except for Mfx, Gfx	Yes, except for Am, Cm	Yes, except for Cfz

(*) Group A: levofloxacin (Lfx), moxifloxacin (Mfx), gatifloxacin (Gfx) / Group B: amikacin (Am), capreomycin (Cm), kanamycin (Km), (streptomycin, S) / Group C: ethionamide (Eto) (or prothionamide, Pto), cycloserine (Cs) (or terizidone, Trd), linezolid (Lzd), clofazimine (Cfz) / Group D1: pyrazinamide (Z), ethambutol (E), high-dose isoniazid (Hh) / Group D2: bedaquiline (Bdq), delamanid (Dlm) / Group D3: p-aminosalicylic acid (PAS), imipenem-cilastatin (Ipm/Cln), meropenem (Mpm), amoxicillin-clavulanate (Amx-Clv), (thioacetazone, T). (Notes: streptomycin is part of the category II retreatment regimen, which should no longer be prescribed according to WHO's latest recommendations (May 2017); registration of isoniazid in regulatory databases was taken into account since it covers regulatory approval of high-dose isoniazid). **(a)** Only upon government declaring an emergency. **(b)** Only if already approved by an SDRA. **(c)** No medicines are registered in Swaziland, but as long as they are registered in South Africa, they can be used in Swaziland.

Group D1 medicines are registered*	Group D2 medicines are registered*	Group D3 medicines are registered*
Yes	No	Yes (Ipm/Cln unknown, Mpm unknown, T unknown)
Yes	Yes, except for Dlm	Yes, except for T
Yes	No	Yes, except for PAS, T
Yes	No	Yes, except for T
Yes	No	Yes, except for PAS, T
Yes [i]	No	Yes (Ipm/Cln unknown, T unknown) [i]
Unknown	No	Unknown
Yes	Yes, except for Dlm	Yes
Unknown [ii]	No	Unknown [ii]
Yes	No	Yes, except for PAS, T
Yes	No	Yes, except for PAS, T
Yes	Yes, except for Dlm	Yes
Yes	No	Yes, except for PAS, Amx/Clv, T
Yes [i]	No	Yes, except for T [i]
Yes	No	Yes
Yes	No	Yes, except for PAS, T
Yes	No	Yes, except for PAS, T
Yes	No	Yes, except for PAS, T
Yes	No	Yes, except for PAS, T
Yes	No	Yes, except for T
NA [iii]	NA [iii]	NA [iii]
Yes	Yes, except for Dlm	Yes, except for T
Yes	Yes, except for Dlm	Yes, except for T
Yes	Yes, except for Dlm	Yes, except for T
No [iv]	No [iv]	No [iv]
Yes	No	Yes, except for T
Yes	No	Yes, except for T
NA [v]	No	NA [v]
Yes	No	Yes, except for T

(i) Answers could not be confirmed. **(ii)** No updated information available on registered medicines in the country. **(iii)** PNG is currently finalising the product registration guidelines. All products listed in the medical and dental catalogue can be procured and imported in the country. **(iv)** No medicines are registered in Swaziland. As a proxy, South Africa is used. When a drug is registered in South Africa, it can be used in Swaziland. **(v)** The TB drugs used by the NTP are included in the Essential Medicines List of Vietnam and TB medicines are exempt from registration and import licensing. Furthermore, national programmes (including the NTP) are not required to register the medicines they use.

LEGEND

Is this policy in place at the national level?

Yes

No

Unknown

NA = Not Applicable

IV. REGULATORY ENVIRONMENT FOR TB MEDICINES

REGULATORY ENVIRONMENT FOR TB MEDICINES: ACCORDING TO NATIONAL POLICY	Unregistered TB drugs are available through compassionate use/other legal mechanisms**	If YES, which one of these mechanisms is in place?	National Essential Medicines List (nEML) reflects WHO recommendations***	Group A medicines are on the nEML***
Afghanistan	●		●	Yes, except for Lfx, Gfx
Armenia	●		● [vi]	Yes, except for Gfx [vi]
Bangladesh	●		●	No
Belarus	●		●	Yes, except for Mfx, Gfx
Brazil	●		●	Yes, except for Gfx
Cambodia	●		●	Yes
CAR	●		●	No
China	●		●	Yes, except for Gfx
DRC	●		●	Yes, except for Gfx
Ethiopia	●	Waiver	●	Yes, except for Gfx
Georgia	●	Compassionate use, regular import procedure, exemption mechanisms, importation for unregistered drugs, under programmatic use	● [vii]	NA [vii]
India	●		●	Yes, except for Gfx
Indonesia	●		●	No
Kazakhstan	?		●	Yes, except for Gfx
Kenya	●		●	Yes, except for Gfx
Kyrgyzstan	●		● [viii]	No [viii]
Mozambique	●		● [ix]	Yes, except for Gfx [ix]
Myanmar	●		●	Yes, except for Gfx
Nigeria	●		●	No
Pakistan	●		●	Yes, except for Mfx, Gfx
PNG	●		●	Yes, except for Mfx, Gfx
Philippines	●		●	Yes, except for Mfx, Gfx
Russian Fed.	●		●	No
South Africa	●		●	Yes, except for Lfx, Gfx
Swaziland	●		●	Yes, except for Gfx
Tajikistan	●	Humanitarian access channel	●	Yes, except for Gfx
Ukraine	●		●	Yes, except for Gfx
Viet Nam	●	Research framework and Expanded Access Program	●	Yes, except for Mfx, Gfx
Zimbabwe	●		● [x]	Yes, except for Gfx [x]

(**) Compassionate use, expanded access programmes, import waivers or other legal mechanisms. **(***)** Group A: levofloxacin (Lfx), moxifloxacin (Mfx), gatifloxacin (Gfx) / Group B: amikacin (Am), capreomycin (Cm), kanamycin (Km), (streptomycin, S) / Group C: ethionamide (Eto) (or prothionamide, Pto), cycloserine (Cs) (or terizidone, Trd), linezolid (Lzd), clofazimine (Cfz) / Group D1: pyrazinamide (Z), ethambutol (E), high-dose isoniazid (Hh) / Group D2: bedaquiline (Bdq), delamanid (Dlm) / Group D3: p-aminosalicylic acid (PAS), imipenem-cilastatin (Ipm/Cln), meropenem (Mpm), amoxicillin-clavulanate (Amx-Clv), (thioacetazone, T). (Notes: streptomycin is part of the category II retreatment regimen, which should no longer be prescribed according to WHO's latest recommendations (May 2017); only medicines listed in anti-TB sections of nEMLs are listed as YES)

Group B medicines are on the nEML***	Group C medicines are on the nEML***	Group D1 medicines are on the nEML***	Group D2 medicines are on the nEML***
Yes, except for Km	Yes, except for Lzd, Cfz	Yes	No
Yes [vi]	Yes, except for Lzd, Cfz [vi]	Yes [vi]	No [vi]
Yes, except for Am, Cm, Km	Yes, except for Eto and Pto, Cs and Trd, Lzd	Yes	No
Yes, except for Am	Yes, except for Lzd, Cfz	Yes	No
Yes, except for Km	Yes	Yes	No
Yes	Yes, except for Lzd, Cfz	Yes	No
Yes, except for Am, Cm, Km	No	Yes	No
Yes	Yes, except for Cs (or Trd), Cfz	Yes	No
Yes	Yes, except for Cfz	Yes	Yes, except for Dlm
Yes	No	Yes	No
NA [vii]	NA [vii]	NA [vii]	NA [vii]
Yes, except for Am	Yes, except for Cfz	Yes	No
Yes, except for Am, Cm, Km	No	Yes, except for Z, E	No
Yes	Yes, except for Eto and Pto, Lzd, Cfz	Yes	No
Yes, except for S	Yes, except for Cfz	Yes	Yes
No [viii]	Yes, except for Lzd, Cfz [viii]	Yes [viii]	No [viii]
Yes, except for Am [ix]	Yes [ix]	Yes [ix]	Yes, except for Dlm [ix]
Yes	Yes, except for Lzd, Cfz	Yes	No
Yes, except for Am, Cm, Km	No	Yes	No
Yes	Yes, except for Cfz	Yes	Yes
Yes, except for Am, S	No	Yes	No
Yes, except for Cm	Yes, except for Eto and Pto, Lzd, Cfz	Yes	No
Yes, except for Am, Km, S	Yes, except for Lzd, Cfz	Yes	Yes, except for Dlm
Yes, except for S	Yes, except for Lzd, Cfz	Yes	Yes, except for Dlm
Yes, except for S	Yes, except for Lzd	Yes	No
Yes	Yes	Yes	Yes
Yes	Yes, except for Cfz	Yes	Yes, except for Bdq
Yes	Yes, except for Lzd, Cfz	Yes	No
Yes, except for Am [x]	Yes, except for Lzd, Cfz [x]	Yes [x]	No [x]

LEGEND

Is this policy in place at the national level?

Yes

No

Unknown

NA = Not Applicable

(vi) The national EML is currently being updated. **(vii)** No valid Georgian National EML exists. It is in the process of being finalised and approved. Meanwhile, WHO EML is used as a reference. **(viii)** The new national EML is currently being approved. **(ix)** Anti-TB medicines are mixed together with other anti-bacterials (no specific anti-TB medicines sublist is reported). **(x)** Latest nEML is from 2011, however medicines present in the guidelines are considered automatically as present in the nEML.

IV. REGULATORY ENVIRONMENT FOR TB MEDICINES

REGULATORY ENVIRONMENT FOR TB MEDICINES: ACCORDING TO NATIONAL POLICY	Group D3 medicines are on the nEML***	Country is enrolled in WHO Collaborative Registration Procedure	Prescriptions are required for TB medicines
Afghanistan	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	No
Armenia	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T [vi]	Yes	Yes
Bangladesh	No	No	Yes
Belarus	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
Brazil	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
Cambodia	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
CAR	No	No	Yes
China	Yes, except for Ipm/Cln, Mpm, T	No	Yes
DRC	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	Yes	Yes
Ethiopia	No	Yes	Yes
Georgia	NA [vii]	Yes	Yes
India	Yes, except for Ipm/Cln, Mpm, T	No	Yes
Indonesia	No	No	Yes
Kazakhstan	Yes, except for T	No	Unknown
Kenya	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	Yes	Yes
Kyrgyzstan	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T [viii]	Yes	Yes
Mozambique	Yes, except for Ipm/Cln, Mpm, T [ix]	Yes	Yes
Myanmar	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
Nigeria	No	Yes	Yes
Pakistan	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
PNG	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
Philippines	Yes, except for PAS, Ipm/Cln, Mpm, Amx/Clv	Yes	Yes
Russian Fed.	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
South Africa	No	Yes	Yes
Swaziland	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
Tajikistan	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	No	Yes
Ukraine	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T	Yes	Yes
Viet Nam	Yes, except for Ipm/Cln, Mpm, Amx/Clv	No	No
Zimbabwe	Yes, except for Ipm/Cln, Mpm, Amx/Clv, T [x]	Yes	Yes

LEGEND

Is this policy in place at the national level?

Yes

No

Unknown

NA = Not Applicable

(***) Group A: levofloxacin (Lfx), moxifloxacin (Mfx), gatifloxacin (Gfx) /v Group B: amikacin (Am), capreomycin (Cm), kanamycin (Km), (streptomycin, S) / Group C: ethionamide (Eto) (or prothionamide, Pto), cycloserine (Cs) (or terizidone, Trd), linezolid (Lzd), clofazimine (Cfz) / Group D1: pyrazinamide (Z), ethambutol (E), high-dose isoniazid (Hh) / Group D2: bedaquiline (Bdq), delamanid (Dlm) / Group D3: p-aminosalicylic acid (PAS), imipenem-cilastatin (Ipm/Cln), meropenem (Mpm), amoxicillin-clavulanate (Amx-Clv), (thioacetazone, T). (Notes: streptomycin is part of the category II retreatment regimen, which should no longer be prescribed according to WHO's latest recommendations (May 2017); only medicines listed in anti-TB sections of nEMLs are listed as YES) **(vi)** The national EML is currently being updated. **(vii)** No valid Georgian National EML exists. It is in the process of being finalised and approved. Meanwhile, WHO EML is used as a reference. **(viii)** The new national EML is currently being approved. **(ix)** Anti-TB medicines are mixed together with other anti-bacterials (no specific anti-TB medicines sublist is reported). **(x)** Latest nEML is from 2011, however medicines present in the guidelines are considered automatically as present in the nEML.

V. PREVENTION

PREVENTION: ACCORDING TO NATIONAL POLICY	TB preventive therapy is provided for adult contacts, child contacts and PLWHA			TB preventive therapy is provided for at-risk populations: prisoners, miners, people with silicosis/diabetes, organ/transfusion recipients	Tuberculin skin or IGRA test must be carried out prior to starting preventive therapy	Preventive therapy regimen is one of the below: A) 6-month INH B) 9-month INH C) 3-month weekly RPT plus INH D) 3-4 month INH plus RIF E) 3-4 month RIF
	PLWHA	Child contacts	Adult contacts			
Afghanistan	?	?	●	Prisoners	✕	A
Armenia	●	●	●		●	A
Bangladesh	?	?	●		●	A
Belarus	●	●	●		●	A
Brazil	●	●	●	People with silicosis/ diabetes, organ/ transfusion recipients	◐ [b]	A, B, E [c]
Cambodia	●	●	●		●	A
CAR	◐	◐	●		●	A, D
China	◐	◐	●		◐	A, C
DRC	◐	◐	●		●	A, B
Ethiopia	●	●	●		●	A
Georgia	●	●	●		● [a]	A (B, C, D, E)
India	◐	◐	●		●	A
Indonesia	?	?	●		?	A
Kazakhstan	●	●	●		●	A
Kenya	●	●	●	Prisoners	●	A
Kyrgyzstan	●	●	●		◐ [b]	A
Mozambique	?	?	●		●	A
Myanmar	●	●	●		●	A
Nigeria	●	●	●		●	A
Pakistan	◐	◐	●		●	A
PNG	◐	◐	●		●	A
Philippines	●	●	●		●	A
Russian Fed.	●	●	●		●	A, D, C
South Africa	?	?	●		●	A
Swaziland	◐	◐	◐	Prisoners, miners, other	●	A
Tajikistan	◐	◐	●		◐ [a]	A
Ukraine	◐	◐	●		◐ [d]	A
Viet Nam	●	●	●		●	A, B
Zimbabwe	●	●	●		●	A, B

LEGEND

Is this policy in place at the national level? ● Yes ● No ? Unknown

If Yes, is the policy being implemented? ● Yes ◐ Yes, but not widely ✕ No ? Unknown

(a) For children only. **(b)** When there is a stockout of TST, IPT can be prescribed without carrying out the test. **(c)** In the process of being implemented, to be introduced in the new guidelines. **(d)** TST done for PLWHA, not known for children.

INH = isoniazid, **RPT** = rifapentine, **RIF** = rifampicin

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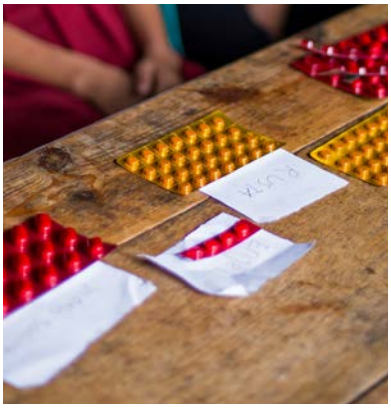

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