OUT OF STEP

DEADLY IMPLEMENTATION GAPS IN THE TB RESPONSE

A survey of TB diagnostic and treatment practices in eight countries

October 2014

ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

www.msfaccess.org

ABOUT 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 healthcare. Founded in 1971, MSF has operations in nearly 70 countries today.

MSF has been involved in tuberculosis (TB) care for 30 years, often working alongside national health authorities to treat patients in a wide variety of settings, including chronic conflict zones, urban slums, prisons, refugee camps and rural areas. MSF's first programmes to treat multidrug-resistant TB opened in 1999, and the organisation is now one of the largest NGO treatment providers for drug-resistant TB. In 2013, the organisation treated 32,000 patients with TB in 24 countries, including 1,950 patients with drug-resistant TB.

ABOUT THE MSF ACCESS CAMPAIGN

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

ADDITIONAL RESOURCES FROM MSF ON TUBERCULOSIS

UNDER THE MICROSCOPE: SOURCES AND PRICES FOR DRUG-RESISTANT TUBERCULOSIS MEDICINES

The third edition of this report, published in 2013, analyses the sources and prices of medicines used to treat drug-resistant tuberculosis (DR-TB), examines the key factors that shape the access environment for DR-TB medicines, reviews the research and development landscape for DR-TB treatment regimens, and makes recommendations for the way forward to reach more people and improve treatment outcomes. The next edition of the report will be published in 2015.

www.msfaccess.org/content/dr-tb-drugs-under-microscope3rd-edition

BEYOND THE MICROSCOPE

This briefing document looks at the issues with existing TB diagnostic tests and the challenges in ensuring that new diagnostic technologies are able to meet programme and patient needs.

http://msfaccess.org/content/beyond-the-microscope

OUT OF THE DARK: MEETING THE NEEDS OF CHILDREN WITH TB

This report outlines the current state of paediatric TB care, looking at current practices, new developments and research needs in paediatric TB diagnosis, treatment and prevention.

http://msfaccess.org/content/out-dark-meeting-needs-of-children-with-TB

TB CRISIS ALERT: THE NEW FACE OF AN OLD DISEASE

This briefing document describes the alarming rise of drug-resistant tuberculosis, the challenges in diagnosing and treating the disease, and what's needed to improve cure rates and stem the epidemic.

http://msfaccess.org/content/tb-crisis-alert

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EXECUTIVE SUMMARY

This is a pivotal time in the fight against tuberculosis (TB), a curable disease that continues to kill more than a million people a year. Amid an emerging drug-resistant TB (DR-TB) crisis, new tools are emerging that offer the potential to strengthen and accelerate the global TB response. How quickly and effectively these will be leveraged to impact the overall TB response is largely dependent upon three factors: effective policies at the national level; full implementation of current WHO guidelines; and access to new drugs and diagnostics.

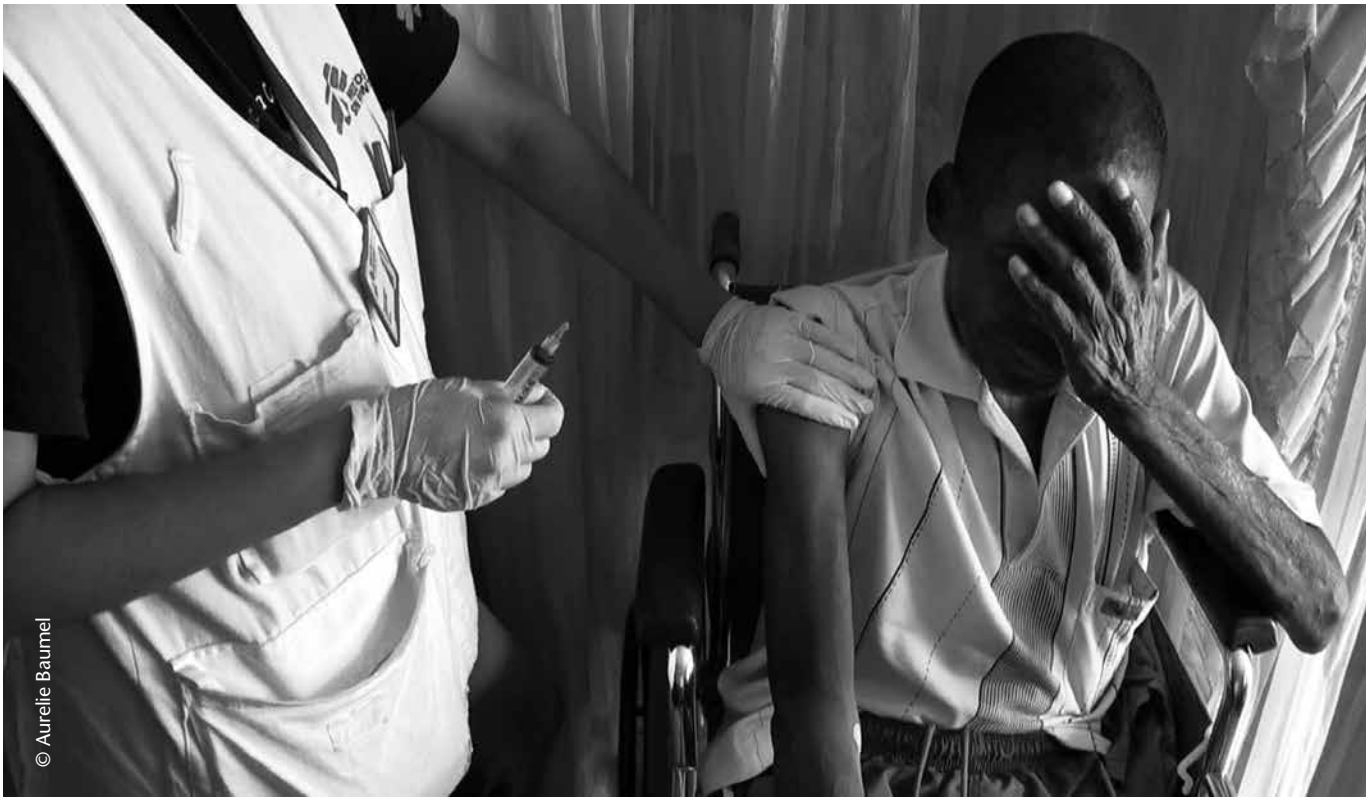
For this report, MSF surveyed TB and DR-TB policies and practices in eight countries with high TB burdens, representing a range of epidemiological, economic, geographic and demographic profiles: Brazil, India, Kenya, Myanmar, Russian Federation, South Africa, Uzbekistan and Zimbabwe. We examined critical indicators for diagnosis, treatment and accessibility of key medicines, drug procurement and funding **[see page 4 for key results]**.

Médecins Sans Frontières (MSF) hopes this report will improve understanding of how current and new guidelines, policies and tools are being implemented on a national level, and whether countries are – or risk – falling out of step with international norms and recommendations.

While this report is not a comprehensive or authoritative assessment of countries' national TB programmes, it provides an indication of the preparedness to implement and scale up use of new diagnostic tools and treatments, as well as new approaches to TB and DR-TB management, that will be required in order to meet the ambitious 20-year targets set in the World Health Organization's (WHO) Global strategy and targets for tuberculosis prevention, care and control after 2015. This report also discusses medicine policies that can stop fuelling drug resistance, and help prepare countries for the adoption of new and more effective drugs and regimens that are on the horizon.

We combine information from published sources with MSF experience in these countries, and make recommendations that could help significantly improve the response and management of drug-resistant TB, in particular.
As the countries surveyed in this report represent a range of different contexts, the recommendations and information provided are hoped to be relevant and valuable to other countries beyond those included here.

Our research found that while there are promising signs of countries' responsiveness to new recommendations and adoption of national policies and practices, there are also alarming gaps in the implementation of these policies – gaps that fuel drug resistance and cost lives.



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Lagging implementation in these countries is indicative of the challenges faced globally by low- and middle-income countries in implementing and funding all the various components for a comprehensive and effective TB programme.

What is clear is that drug-resistant forms of the disease will continue to spread unabated unless a stronger and more concerted effort to scale-up DR-TB services, in step with the implementation of optimal tools, guidelines and policies, is made at the country level. Too many people sick with TB will remain undiagnosed, receive substandard care and/or inadequate treatment or no treatment at all. Cure rates for DR-TB will remain abysmal, drug-resistant strains will continue to emerge and spread, and the death count will grow.

Adoption by WHO member states of the ambitious 20-year global TB targets has set the stage for an ambitious international response. Now countries and global health actors at every level must step up their commitment and actions to ensure major strides are taken in the post-2015 fight against TB, and in particular against the emerging global DR-TB epidemic.

CARRYING FORWARD THE DR-TB MANIFESTO CAMPAIGN

As an advocate for people affected by DR-TB around the world, Phumeza Tisile delivered the 'Test Me, Treat Me' DR-TB Manifesto petition to the World Health Assembly in May 2014, where delegates committed their governments to implementing the new 20-year global TB strategy.

Phumeza, a 23-year old South African who survived XDR-TB, and her MSF doctor Jenny Hughes, had written the DR-TB Manifesto more than a year prior, setting out the demands of patients and medical staff for universal access to diagnosis and treatment, rapid development of better treatment regimens, and full funding of these efforts. More than 55,000 patients, doctors and other supporters signed the petition supporting better DR-TB care.

The urgent demands of patients and doctors are at the core of MSF's continuing advocacy on DR-TB towards governments, funders, researchers and pharmaceutical companies. This report marks a transition to greater country-level advocacy aimed at radically improving survival rates of those afflicted by DR-TB.

THE EMERGING DRUG-RESISTANT TB CRISIS

DR-TB is an emerging public health crisis in many countries. MDR-TB is increasingly being found in patients with no history of TB treatment, indicating that resistant strains of the disease are being transmitted from person to person. In our own clinics, MSF is seeing more people presenting with MDR-TB as their initial diagnosis. In Uzbekistan, for example, MSF diagnoses MDR-TB in up to 40% of patients who have never been treated for TB before.[1]

Globally, the number of MDR-TB cases reported in 2012 accounted for less than one-third of the true number of MDR-TB cases, which is estimated to be 450,000.[2] Although nearly 94,000 reported TB cases were eligible for MDR-TB treatment, only about 77,000 people were placed on treatment.[2] For those on MDR-TB treatment, the cure rate is less than 50% – due in part to high levels of mortality and large numbers of patients being lost to follow-up.[2] Even within MSF projects, where new tools and patient-focused treatment approaches have been implemented, the overall cure rate for MDR-TB is just 56% and only 27% for XDR-TB patients.[3]

However, recent advances in treatment and diagnostics have the potential to improve the global response to the epidemic. After nearly 50 years without any new classes of drugs developed for TB, there are now two new classes of drugs registered specifically for use in drug-resistant TB – although routine use of these new drugs is likely still many years away. MSF has begun providing one of these new drugs, bedaquiline, to a limited number of patients through compassionate use programmes or on an individualised basis according to national regulations **[see page 16]**.

An assessment of where countries are in their response to the DR-TB epidemic is necessary to ensure that the benefits of the latest tools and policies are maximised and new advances in TB care can be implemented quickly.

CRITICAL GAPS IN THE DR-TB RESPONSE

MSF's research for this report indicates that while countries are responding to new recommendations, rates of adoption and implementation vary greatly, and a number of critical gaps, in particular in the response to drug-resistant TB, are cause for alarm.

KEY RESULTS: FIVE DEADLY GAPS:

DIAGNOSTIC GAPS FOR DR-TB:

Laboratory-confirmed diagnosis is critical to reducing the number of people misdiagnosed and receiving wrong or inadequate treatment for undetected DR-TB. But access to drug susceptibility testing (DST) for first-line and second-line TB drugs remains limited. In five out of the six countries that provided data on DST coverage, fewer than 40% of previously treated cases are tested for first-line DST and less than 15% of MDR-TB cases are tested for second-line DST.

TREATMENT GAPS FOR DR-TB:

Correctly and promptly treating DR-TB patients is crucial to containing the spread of drug resistance. But in four of eight countries, fewer than 75% of MDR-TB cases detected were enrolled in treatment.

OUTMODED MODELS OF CARE:

Four out of eight countries still include some form of routine hospitalisation for DR-TB patients in their guidelines, in spite of the fact that ambulatory or community-based care models have similar outcomes to hospital/centralised-based care while offering greater cost-effectiveness and a more tolerable experience for the patient.

LIMITED ACCESS TO NEW AND REPURPOSED DRUGS:

Despite the recent approval of two new TB drugs, the countries surveyed have had limited access to only one of the new drugs, and only through compassionate use or equivalent programmes. Six out of eight countries have the necessary regulations to allow patients to access new drugs via compassionate use or equivalent programmes. No country had all Group 5 medicines incorporated in the national essential medicines list. Group 5 drugs have unclear efficacy for TB, but are critically important as components of therapy for XDR-TB.

SEVERE UNDERFUNDING:

Five of the countries surveyed have a funding gap in their national TB programmes. The three low-income countries surveyed (Kenya, Myanmar and Zimbabwe) face the most severe funding gaps for their national TB programmes, with less than 50% of required funding available.

High DR-TB Burden

Low DR-TB Burden

BRAZIL
Upper-middle-income
Pop: 199 million
TB Incidence: 46/100,000

Low DR-TB burden:
- 684 MDR-TB cases*
- New MDR-TB cases: 1.4%
- Re-Rx MDR-TB cases: 7.5%

High HIV burden:
- Adult HIV prevalence: 0.30%
- HIV+ TB patients: 20%

* Lab-confirmed MDR-TB cases
All country income classifications from World Bank (http://data.worldbank.org/about/country-and-lending-groups)
All adult HIV prevalence data from CIA World Factbook (https://www.cia.gov/library/publications/the-world-factbook)
All other data from World Health Organization (Global TB Report 2013 and www.who.int/tb/data)

SUMMARY COUNTRY DATA

INDIA
Lower-middle-income
Pop: 1,237 million
TB Incidence: 176/100,000

High DR-TB burden:
- 16,588 MDR-TB cases*
- New MDR-TB cases: 2.2%
- Re-Rx MDR-TB cases: 15%

High HIV burden:
- Adult HIV prevalence: 0.30%
- HIV+ TB patients: 5%

UZBEKISTAN
Lower-middle-income
Pop: 29 million
TB Incidence: 78/100,000

High DR-TB burden:
- 1,728 MDR-TB cases*
- New MDR-TB cases: 23%
- Re-Rx MDR-TB cases: 62%

Low HIV burden:
- Adult HIV prevalence: 0.10%
- HIV+ TB patients: 5%

RUSSIAN FEDERATION
High-income
Pop: 143 million
TB Incidence: 91/100,000

High DR-TB burden:
- 13,612 MDR-TB cases*
- New MDR-TB cases: 23%
- Re-Rx MDR-TB cases: 49%

High HIV burden:
- Adult HIV prevalence: 1%
- HIV+ TB patients: not reported

MYANMAR
Low-income
Pop: 53 million
TB Incidence: 377/100,000

High DR-TB burden:
- 788 MDR-TB cases*
- New MDR-TB cases: 4.2%
- Re-Rx MDR-TB cases: 10%

High HIV burden:
- Adult HIV prevalence: 0.60%
- HIV+ TB patients: 27%

SOUTH AFRICA
Upper-middle-income
Pop: 52 million
TB Incidence: 1,003/100,000

High DR-TB burden:
- 15,419 MDR-TB cases*
- New MDR-TB cases: 1.8%
- Re-Rx MDR-TB cases: 6.7%

High HIV burden:
- Adult HIV prevalence: 17.9%
- HIV+ TB patients: 65%

ZIMBABWE
Low-income
Pop: 14 million
TB Incidence: 562/100,000

Low DR-TB burden:
- 149 MDR-TB cases*
- New MDR-TB cases: 1.9%
- Re-Rx MDR-TB cases: 8.3%

High HIV burden:
- Adult HIV prevalence: 14.7%
- HIV+ TB patients: 70%

KENYA
Low-income
Pop: 43 million
TB Incidence: 272/100,000

Low DR-TB burden:
- 225 MDR-TB cases*
- New MDR-TB cases: 2.5%
- Re-Rx MDR-TB cases: 10%

High HIV burden:
- Adult HIV prevalence: 6.1%
- HIV+ TB patients: 39%

METHODOLOGY

This report provides summary results of a survey conducted by MSF in eight countries. Information was collected from March to July 2014 on 30 key indicators related to TB care. The eight countries, Brazil, India, Kenya, Myanmar, the Russian Federation, South Africa, Uzbekistan and Zimbabwe, represent a broad spectrum of the epidemiology of TB, DR-TB and HIV co-infection, aas well as a range of World Bank income classifications. By surveying a variety of different contexts, MSF hopes the results will be useful beyond the countries surveyed. MSF is currently treating TB in all surveyed countries except Brazil.

As part of the survey, MSF collected data from government sources and published documents from reliable national and international sources, including national HIV and TB guidelines, national treatment guidelines (standard treatment guidelines and essential medicines lists) and national programme updates from departments responsible for TB. Where reliable and recent data could not be obtained from national documents, MSF conducted interviews with national authorities and/or used other verifiable information. Where relevant, MSF's direct experience in providing care in country supplemented the other data collected. International sources were also used, including primarily the 2013 WHO Global Tuberculosis Report.

In some cases, there is a delay between the establishment of normative best practices and adopting them into revised national guidelines. During the research process, MSF was made aware that some national guidelines were under revision,[a] and where we could validate this – for example, by reviewing the draft guidelines – we have noted any relevant information. However, information from unpublished or draft guidelines was not applied in our analysis.

It is important to also note that even when national guidelines reflect new normative standards, implementation may lag. Delays and other implementation challenges are difficult to quantify with reliable sources, but direct MSF experience and key informant interviews were used to inform our analysis, where applicable.

Accessing reliable and up to date information was a challenge throughout the data collection process. In some cases, multiple actors were approached to find verifiable information, but this information was not always available and some questions remain unanswered. For some indicators, country data is from different years, hindering rigorous comparisons. Where data used are more than three years old, this is indicated in the text.

As an emergency medical humanitarian organisation, it is not within MSF's purview to validate officially reported figures or data.

Key survey results discussed in this report are summarised in the Annex. Citations for the sources of survey results, along with the complete survey results, are available at: www.msfaccess.org/outofstep/

a. Myanmar, Uzbekistan, Russian Federation and South Africa have new policies for TB in draft, some with lengthy delays in approval. For example, Uzbekistan's unified national TB guidelines have been in draft process for over three years.

ENSURING ACCURATE AND TIMELY DIAGNOSIS: A FIRST STEP IN ENSURING EFFECTIVE TREATMENT FOR PATIENTS

In spite of recent advances in diagnostics technology and new WHO recommendations regarding their use, significant gaps remain in the early detection of TB cases and in the implementation of proper diagnostic work-up for presumptive TB and DR-TB cases. Increased access to laboratory-confirmed diagnosis is critical to reduce the numbers of missed TB cases, of people misdiagnosed and treated unnecessarily based on empirical evidence, and of people receiving wrong or inadequate treatment because their DR-TB remains undetected.[2] This section reviews key diagnostic indicators across the countries that can help assess readiness for scale-up.

MSF's survey found that:

- Five countries fall below Global Plan to Stop TB (2011–2015) targets for the number of laboratories performing culture and drug susceptibility testing (DST);
- All countries have introduced Xpert MTB/RIF, but roll-out and plans for scale-up vary;
- In most of the countries, coverage for first-line and second-line DST remains far below the targets set by the Global Plan to Stop TB (2011–2015); second-line DST capacity exists in six countries, but access to DST across the board is too low; and
- In all countries surveyed, na tional guidelines have incorporated WHO guidance for diagnosis of drug-resistant TB, including the latest recommendations released on the use of Xpert MTB/RIF.

Active case finding and contact tracing are important strategies to further increase TB case detection. The inclusion of recommendations for active case finding and contact tracing strategies in the national guidelines of all countries surveyed represents a positive and necessary initial step.[b] While it was not possible for MSF to assess the extent of implementation of these strategies, it is important that national TB programmes (NTPs) monitor this.

ACCESS TO LABORATORY-BASED TB DIAGNOSIS AND COVERAGE OF DST

According to the WHO Global TB Report 2013, only 57% of the 4.6 million new pulmonary TB patients notified in 2012 were bacteriologically confirmed using a WHO-recommended diagnostic algorithm.[c] Data collected for this report are in line with global data showing that the proportion of TB cases with laboratory-confirmed diagnosis is low and varies widely across countries, ranging from 34% in Myanmar to 69.9% in Brazil. Data for Myanmar, Russian Federation (from 68 of 83 territories), Uzbekistan and Zimbabwe suggest that less than 50% of notified TB cases had a laboratory-confirmed diagnosis.

Given that clinical diagnosis still plays an important role in TB due to the limited capacity of available tools to diagnose more complex manifestations of the disease (such as HIV-associated TB, paucibacillary TB, extrapulmonary TB), it is expected that a proportion of notified TB cases are diagnosed based only on symptoms and clinical judgement, and lack laboratory confirmation.

Even taking into consideration the role played by clinical diagnosis in the management of TB cases, the proportion of cases lacking laboratory-confirmed diagnosis reported by several surveyed countries is significant, and suggests that poor access to laboratory-based diagnostic work-up, among other causes, plays an important role. In addition, the WHO Global TB report 2013 indicates that about three million TB cases have not been diagnosed or notified. Thus overall, these data confirm that access to laboratory-based diagnosis for TB needs to be strengthened. Scale-up of Xpert MTB/RIF could help fill this gap by increasing the proportion of bacteriologically-confirmed TB cases among TB cases started on treatment, as evidenced in recent randomised clinical trials.[4,5]

b. Target populations for these interventions vary slightly between countries, depending on the epidemiological profiles. Refer to full survey of results online: msfaccess.org/outofstep

c. *M. tuberculosis* is detected on biological specimen by sputum smear microscopy, culture or WHO-approved rapid nucleic acid amplification based-diagnostics, such as Xpert MTB/RIF.

Continued overleaf

Specifically for DR-TB diagnosis, the Global Plan to Stop TB (2011–2015) set targets of testing 20% of new cases and 100% of previously treated cases for resistance to first-line anti TB drugs, and testing 100% of confirmed MDR-TB cases for resistance to second-line drugs by 2015. In addition, the plan includes a target of 100% of confirmed MDR-TB cases enrolled into treatment by 2015.[6] The new post-2015 strategy[7] sets even more ambitious targets for DR-TB diagnosis, calling for universal DST.[8]

In all eight countries surveyed for this report, national guidelines recommend first-line DST be performed at least for high-risk groups, and first-line and second-line DST be performed for any rifampicin-resistant cases detected by Xpert MTB/RIF, in accordance with WHO guidance.[d] However, most countries surveyed are far from reaching the targets in the Global Plan to Stop TB (2011–2015) for testing patients for MDR-TB among new and retreatment cases.

The 2013 WHO Global TB Report indicates that access to first-line DST is particularly poor in Brazil, Kenya, and Zimbabwe, with only 2%, <1% and 3% of new cases, and 2%, 12% and 6% of retreatment cases being tested for MDR-TB, respectively. Access is better in former Soviet Union (FSU) countries with 79% of new cases and 24% of retreatment cases tested for MDR-TB in the Russian Federation, and 52% of new cases and 39% of retreatment cases tested for MDR-TB in Uzbekistan. In both countries, targets for the proportion of new cases tested for MDR-TB have been met, while access to first-line DST for retreatment cases needs significant strengthening in order to meet the 100% target by 2015. Data were not available for India, Myanmar or South Africa.


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However, based on available data for India, where culture and DST are not routinely performed for new cases, MSF calculates that approximately 60% of retreatment cases are tested for MDR-TB.[e]

Access to second-line DST testing appears to be more challenging in most of the countries surveyed. In South Africa, 72% of MDR-TB patients were tested for second-line DST in 2012. In Myanmar, second-line DST is not performed systematically, and only 10.8% of MDR-TB cases were tested in 2012. In Kenya, it was not possible to quantify the number of MDR-TB cases tested for second-line DST; second-line DST is also not systematically conducted in this country, despite national guidelines recommending second-line DST for all MDR-TB patients. Numbers were also low for Brazil, Uzbekistan, and particularly for India, where only 12.3%, 10% and 3.6% of MDR-TB patients underwent second-line DST testing, respectively.[f] Data were not available for the Russian Federation and not applicable for Zimbabwe.[g]

IN-COUNTRY LABORATORY CAPACITY FOR DR-TB DIAGNOSIS AT REFERRAL LEVEL

Many of the countries surveyed do not have enough laboratories performing culture and DST to achieve the diagnosis coverage targets outlined in the Global Plan to Stop TB (2011–2015) released by the Stop TB Partnership. In more than half of the countries surveyed (India, Kenya, Myanmar, Uzbekistan and Zimbabwe), the number of laboratories performing culture and DST remains below the 2015 target of one laboratory for culture and DST per five million people.[6] India and Myanmar fall far short, with only 0.2 culture and DST laboratories per five million people. Among the countries that have not yet met the current Global TB Plan targets, Kenya and Myanmar have indicated plans to scale up culture and DST laboratory capacity with the help of external donors. In the majority of countries surveyed, further investments are needed to ensure enrolment in external quality assessment (EQA) programmes for DST, and to increase

d. For India, the information regarding which patients' groups should be tested for first-line and second-line DST has been taken from the publication entitled Standard of Care in India and available at http://www.tbonline.info/media/uploads/documents/214586958-standards-for-tb-care-in-india-2014.pdf. Recommendations in this document have not yet been included in the national guidelines.

f. 2013 data used for Brazil and Uzbekistan. 2012 data used for India.

g. Note that Zimbabwe does not have in-country second-line DST capacity, but falls below MDR-TB case threshold, per WHO guidance.

e. Based on data obtained via right to information request and the number of notified retreatment cases reported in the WHO Global TB report 2013, MSF calculated coverage using the total number of LPAs and culture DST tests performed in 2012, using assumption that each test performed represented one additional case tested. This may overestimate the number of cases tested, because the number of culture performed includes testing of other patient categories in addition to the retreatment cases (HIV/TB coinfected patients, DR-TB contacts, failures).

the number of laboratories that have an accredited quality management system in place.

Six countries surveyed have in-country capacity to perform second-line DST. Zimbabwe does not have second-line DST capacity in country, but falls below the threshold of MDR-TB cases for which WHO recommends implementing second-line DST in country.[h] Myanmar has recently scaled up capacity of its national TB reference laboratory (NTRL) to perform second-line DST, with plans to have two second-line DST laboratories by 2016. However, neither laboratory was fully operational at the time of data collection for this report.[9]

Seven of the countries surveyed have implemented line probe assays (LPAs), which are high-throughput molecular tests that can be implemented at central and regional level and can be used for rapid detection of resistance to rifampicin and isoniazid. (In Russian Federation, use of LPAs was not confirmed.) However, implementation of this technology for rapid detection of drug resistance remains limited, with only South Africa having more than one laboratory per five million population using this assay.

UPTAKE, ROLLOUT, AND SCALE-UP OF XPERT MTB/RIF

Endorsed by WHO in December 2010, Xpert MTB/RIF is the first molecular test that can be used for simultaneous detection of TB and rifampicin resistance that is suitable for implementation at a decentralised level (such as a district-level facility). The implementation of this new rapid diagnostic test is increasing TB case identification and helping to uncover the reach of both TB and DR-TB worldwide, although a number of challenges to wider implementation remain.[10, 11]

All countries surveyed in this report have begun implementing Xpert MTB/RIF, but its placement in the diagnostic algorithm and the scale of roll-out vary greatly among countries.

South Africa has replaced smear microscopy with Xpert MTB/RIF as the initial diagnostic test for all presumptive TB cases. Brazil and the Russian Federation have also adopted diagnostic algorithms that recommend use of Xpert MTB/RIF (and/or other molecular based tests, in the case of the Russian Federation) as the initial diagnostic test for all presumptive TB cases.

POSITIVE RESULTS FROM MSF'S XPERT MTB/RIF IMPLEMENTATION

By April 2013, MSF had implemented Xpert MTB/RIF in 23 countries. Data collected through routine implementation indicates that the introduction of Xpert MTB/RIF in MSF projects led to significant increases in laboratory-confirmed TB cases and decreases in time to treatment initiation.[16] Specifically, the introduction of Xpert MTB/RIF into MSF TB projects has resulted in three key improvements:

1 Increased number of TB cases with laboratory-confirmed diagnosis

Following MSF's implementation of Xpert MTB/RIF in different epidemiological settings throughout a pilot phase, laboratory-confirmed TB cases increased overall by around 42% – with large variations across sites – compared to sputum smear microscopy.[17] WHO expects the introduction of Xpert MTB/RIF to lead to a three-fold increase in the detection of rifampicin-resistant TB cases detected.[18]

2 Expedited time to treatment

Use of Xpert MTB/RIF led to a marked decrease in time between diagnosis and treatment initiation. Most patients with detected rifampicin resistance were started on empiric MDR-TB treatment with a median delay of 7 to 17 days from the first specimen collection, when tested using Xpert MTB/RIF in MSF's monitored projects.[19, 20] For example, in Swaziland, Xpert MTB/RIF reduced the time from sample collection to DR-TB treatment initiation from an average 65.9 days with a conventional diagnostic algorithm, to an average of just 13.9 days using Xpert MTB/RIF as an initial diagnostic test.[21]

3 Improved diagnoses for people with HIV/TB co-infections

Xpert MTB/RIF improved detection of TB by at least 20% over smear microscopy. In settings with a high prevalence of HIV, by adding Xpert MTB/RIF testing to smear microscopy, the relative gain in the detection of laboratory-confirmed TB cases among people living with HIV is 27% in Kenya, and 76.8% in Swaziland. The gain of replacing microscopy with Xpert MTB/RIF is 21.2% in Kenya and 70.5% in Swaziland.[19]

h. In order to retain proficiency and expertise, it is recommended that second-line DST only be performed if at least 200 specimens from high-risk patients are expected per year. For details see: A Roadmap for Ensuring Quality Tuberculosis Diagnostics Services within National Laboratory Strategic Plans: http://www.stoptb.org/wg/gli/assets/documents/GLI%20Roadmap%20First%20Issue%202010110.pdf

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In the facilities that have implemented Xpert MTB/RIF in Uzbekistan, this assay is used as the initial diagnostic test on all presumptive TB cases, but roll-out of the new technology remains limited. The remaining four surveyed countries are using Xpert MTB/RIF as the initial diagnostic test only for high-risk groups.[i] While this is consistent with WHO recommendations, it may also be reflective of limited resources for further scale-up.[12] Unfortunately, uptake of the latest WHO recommendations regarding the use of Xpert MTB/RIF for the diagnosis of select forms of extra-pulmonary TB (EP-TB) is still limited.[j]

Available data show that Brazil, India, South Africa, Kenya and Zimbabwe increased the number of Xpert MTB/RIF devices implemented through 2013.[13] South Africa has reached sufficient capacity to meet 100% of diagnostic needs with Xpert MTB/RIF in the public sector, replacing smear microscopy,[14] while in Brazil implementation of a nationwide plan to roll-out Xpert MTB/RIF as replacement of smear microscopy is underway.[15] Roll-out of Xpert MTB/RIF is progressing more slowly in Kenya, Zimbabwe, India, Myanmar, Russian Federation and Uzbekistan.

Three key challenges in rolling out Xpert MTB/RIF were consistently highlighted across countries surveyed: upgrading laboratory infrastructure; ensuring adequate staff training; and implementing an efficient supply management system. In the Russian Federation, the reported main challenge for Xpert MTB/RIF rollout is the unacceptably high price of test cartridges **[see box below]**.

Further scale-up of Xpert MTB/RIF is planned in at least seven countries. Reliable information was not available for Zimbabwe. The extent of future scale-up varies considerably between countries and partially depends on the rollout coverage that has been achieved so far. For instance, Brazil is planning to provide 50 additional devices to complete replacement of sputum smear microscopy as an initial diagnostic test, while South Africa is now focusing on expanding use of Xpert MTB/RIF in special settings such as correctional facilities and the mining sector.

Kenya and India plan to significantly increase capacity for Xpert MTB/RIF testing by 2016; Kenya is planning to reach a total of 440 devices implemented by 2016, and India's National Strategic Plan calls for 1,039 additional devices to be implemented by the same year. By contrast, the rollout of Xpert MTB/RIF in Myanmar and Uzbekistan is progressing at a much more moderate pace and to the best of our knowledge there are no ambitious plans for scale-up. Myanmar plans to implement 14 additional devices by the end of 2014. Uzbekistan plans to implement six additional devices, but the timeframe is unknown.

DIAGNOSTIC CARTRIDGES, KITS AND REAGENTS: UNEVEN AND OPAQUE PRICES

Information on prices paid by national TB programmes (NTPs) and the public sector for Xpert MTB/RIF cartridges and other kits and reagents for the WHO-endorsed commercial tests (Genotype MTBDRplus, and BBL tubes for Mycobacteria Growth Indicator Tubes (MGIT)) was very difficult to obtain due to a lack of clear and reliable records.

Although there is a list of countries eligible for preferential pricing,[22] we sought confirmation on the actual price paid for Xpert MTB/RIF cartridges, which could only be established for Brazil, Myanmar, Zimbabwe and the Russian Federation. While in the first three countries the public sector has access to the preferential price of US$9.98 negotiated for high burden countries,[22] in the Russian Federation this price is reportedly not accessible and the NTP pays $60 per Xpert MTB/RIF cartridge procured through the local distributor. This is six times higher than the $9.98 ex-works negotiated price to which the Russian Federation should have access. Although ex-works prices do not include additional costs such as transport-related costs, importation taxes and customs clearance, these extra costs cannot justify a six-fold increase in the final price charged to the public sector. It is critical to ensure that high-burden countries have access to the lowest negotiated prices. Transparency of the final prices paid by NTPs and governments is essential in order to leverage and monitor access to negotiated prices.

i. For example, patients at risk of DR-TB and HIV-associated TB. (India and Zimbabwe are also using Xpert MTB/RIF as an add-on test to sputum smear microscopy (SSM) in smear-negative presumptive TB cases.)

j. Refer to full survey of results online: msfaccess.org/outofstep

IMPROVING TREATMENT OUTCOMES: ADOPTION OF EFFECTIVE STRATEGIES AND ENSURING ACCESS

Effectively managing TB and DR-TB treatment requires ensuring that patients are getting the right treatment at the right time, ideally at no charge and close to where they live. Efforts to properly treat MDR-TB are complicated by the fact that the treatment is long, complex and expensive, with poor outcomes and high rates of loss to follow-up. But until a new regimen is developed,[23] governments must scale up today's treatment in order to close the deadly gaps between diagnosed cases and those put on treatment, particularly for MDR-TB and XDR-TB.

This section assesses implementation of treatment policies and practices that could help curb the epidemic, such as scaling up access to DR-TB treatment, ensuring all diagnosed patients start treatment, implementing WHO recommendations for management of re-treatment cases, introducing daily dosing for drug-sensitive TB (DS-TB) treatment, reducing hospitalisation, and decentralising treatment initiation.

MSF's survey found that:

- Brazil and Kenya had the highest reported MDR-TB treatment initiation rates at 100%. Myanmar and South Africa had the lowest at 56% and 42%, respectively;
- Four countries still recommend routine hospitalisation for DR-TB, with the Russian Federation still recommending routine hospitalisation for smear-positive DS-TB;
- Two countries still recommend intermittent dosing throughout treatment for DS-TB regimens;
- Five countries still use the Category 2 re-treatment regimen, and three of these countries have high MDR-TB burdens; and
- In policy, implementation and treatment options, paediatric patients are being left behind.

DRUG–RESISTANT TB TREATMENT GAP

As described already in this report, many people with TB or DR-TB, especially in the case of HIV/TB co-infection, are not properly diagnosed. However, of those cases with bacteriologically-confirmed TB, more than 90% received treatment in countries for which data were available.[k] Myanmar was an exception, with only one-third of bacteriologically-confirmed cases starting treatment.

For DR-TB, the number of patients diagnosed is increasing, but treatment initiation is not keeping pace, putting immense pressure on already struggling DR-TB treatment programmes. Scale up of Xpert MTB/RIF has contributed to an increase in case detection of 42% in 2012 over the previous year,[2] but this was associated with an increasing treatment gap, with only 25% of estimated MDR-TB patients starting treatment globally.[2]

Of the countries surveyed, only Brazil and Kenya report meeting the Global Plan to Stop TB (2011–2015) target of 100% of detected cases started on MDR-TB treatment. Zimbabwe, India and Uzbekistan enrolled 70%, 85% and 86% of diagnosed MDR-TB cases into treatment respectively, indicating that strengthening is needed in order to ensure patients are not lost to follow-up.

Significant challenges are faced by Myanmar and South Africa where only 56% and 42% of patients with detected MDR-TB were started on treatment in 2012, respectively.

In the Russian Federation there were more MDR-TB patients started on treatment than had laboratory-confirmed diagnosis, with 26% of treated patients lacking a laboratory confirmation. Starting patients on DR-TB treatment without a confirmed diagnosis and known resistance pattern also occurs in India, where an increasing proportion of patients are started on XDR-TB treatment without a recorded laboratory confirmation of XDR-TB (35% in 2013, up from 15% in 2012). This could be due to poor reporting of laboratory results. More worryingly, this could be due to a high rate of empirical treatment, which could be a consequence of the poor access to second-line DST described previously in this report **[see page 8]**.[24] While there are circumstances requiring patients to be started on MDR-TB treatment without a confirmed diagnosis (i.e., for children, extrapulmonary TB, HIV co-infection, etc.), it is critical to ensure that patients receive a confirmed diagnosis where possible and are put on the appropriate treatment for DR-TB in order to improve treatment outcomes, and ensure no further resistance is generated.

k. Note that data for Russian Federation are from 2010.

Continued overleaf

Myanmar was the only country surveyed with an official registry/waiting list of patients for MDR-TB treatment, with more than 1,500 listed in 2013. As only two countries are starting all diagnosed patients on treatment, it is important that patients who are diagnosed but not initiated on treatment are recorded. Recorded or not, those waiting are effectively being left to die without access to the appropriate treatment. Delaying patient access to treatment puts communities at risk of the spread of MDR-TB from patients unable to access the treatment they need.

DAILY DOSING AND REMOVAL OF CATEGORY 2

WHO now recommends daily dosing for DS-TB wherever feasible.[25, 26] Although not ideal, intermittent dosing (three times per week) can be used during the continuation phase if each dose is directly observed. India and Uzbekistan still use intermittent treatment. For India, intermittent treatment is used during both the intensive and continuation phase. Uzbekistan still uses seasonal/non-DOTS treatment regimens (intermittent, or categorized as 'Cat zero');[I] however, the trend has been decreasing over the past couple of years. A recent study in India showed that within the intermittent dosing group there was a higher rate of loss to follow-up,[27] adding to the associated risk of resistance generation.[27]

The 2010 WHO guidelines recommend that Category 2 re-treatment regimen, which adds one drug to a potentially failing regimen, only be considered for areas with a low risk of MDR-TB or as an interim measure in countries that have not yet achieved the Global Plan to Stop TB (2011–2015) target of all previously-treated patients having access to DST at the start of treatment.

Five countries have the Category 2 re-treatment regimen in their guidelines (India, Kenya, Myanmar, Uzbekistan and Zimbabwe). Three of these countries (India, Myanmar and Uzbekistan) have high MDR-TB burdens. The Category 2 regimen has been shown to have poor outcomes in countries with high rates of MDR-TB and high HIV co-infection rates.[I] Data show streptomycin resistance at levels above 20% in Uzbekistan[28] and India,[29, 30] and at only slightly lower levels in Myanmar.[31]

REDUCING HOSPITALISATION AND DECENTRALISING TREATMENT INITIATION

WHO recommends patients with MDR-TB be treated using mainly ambulatory or community-based models of care, rather than models of care based principally on hospitalisation. Increasing evidence shows the treatment outcomes are similar with additional benefits, including cost effectiveness.[32]

Four countries still include routine hospitalisation recommendations in their guidelines for drug-resistant TB. India recommends a minimum of a week, and South Africa recommends hospitalisation for smear-positive cases until they have two consecutive negative smears. The Russian Federation and Uzbekistan recommend routine hospitalisation for all MDR-TB patients until sputum conversion, which depending on criteria used in country, could be for six months or more. The Russian Federation also recommends routine hospitalisation for smear-positive DS-TB. In the Karakalpakstan region of Uzbekistan, where MSF is working, the majority of the patients are started on ambulatory care from day one, while hospitalisation is reserved for those meeting certain criteria (e.g. critically ill patients). With the experience of ambulatory care from Karakalpakstan, the Ministry of Health plans to shift from hospitalisation to out-patient care.

Medicines and hospitalisation contribute up to 90% of the cost of DR-TB care.[33] The cost of drugs are still prohibitively expensive at $1,500–$3,000 per patient per treatment course,[34] despite the fact that since 2012 prices have decreased by 23% for a regimen using cycloserine and 11% for a regimen using PAS.[35] Decentralisation of care could significantly decrease the total cost of treating MDR-TB **[see page 13]**,[36, 37] while also decreasing loss to follow-up rates[38] without negatively affecting outcomes.[36, 32]

Among the eight countries surveyed, levels of care for MDR-TB treatment initiation vary. South Africa endorsed a decentralised model of care in 2011, whereby treatment may be started at sub-district level hospitals, however in some areas (in Kwa-Zulu Natal and Western Cape provinces) DR-TB management has been decentralised even further to a primary care level. Furthermore, preparations to implement nurse-initiated MDR-TB treatment at specific sites in all provinces have begun.[39] Kenya allows enrolment at health facility level three (health centre), and Zimbabwe at district level hospitals.

In the remaining countries, patients are started on MDR-TB treatment in regional hospitals or in specialised DR-TB centres, illustrating the need for further efforts to decentralise MDR-TB care.

I. Intermittent treatment is given seasonally, doesn't depend much on intensive or continuation phase, but mostly patients are given a single TB drug or two TB drugs for a non-specified period of time or for a duration of 4–6 months (as continuation phase).

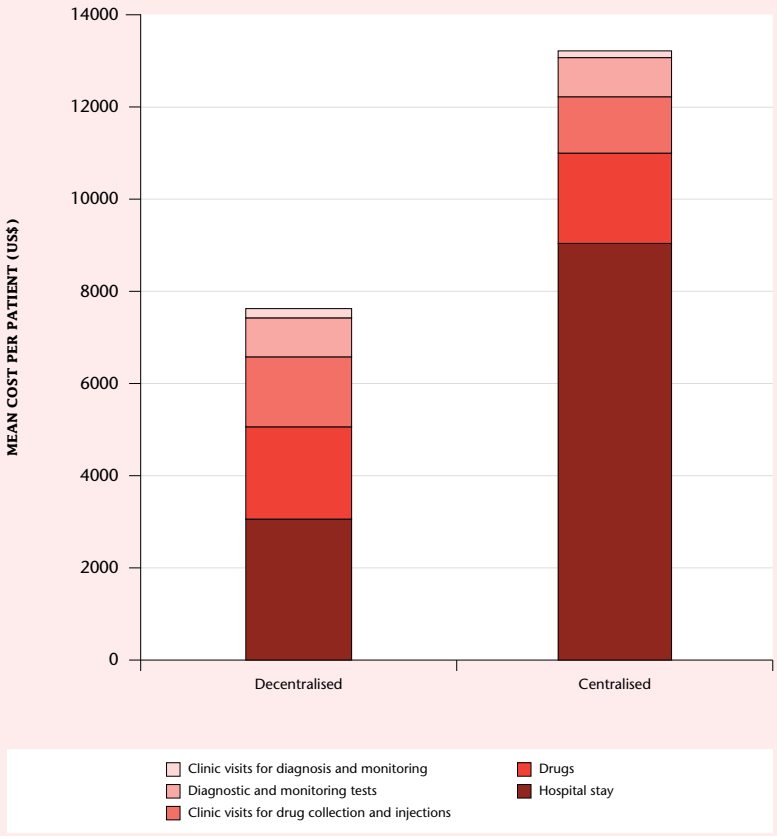
BOX 1: DECENTRALISED DR-TB TREATMENT IMPROVES OUTCOMES AND REDUCES COSTS

In some countries requiring routine hospitalisation, MSF is working with ministries of health (MOHs) and sharing MSF's experience of implementing patient-centred decentralised models of care.

In Uzbekistan, MSF has been working in close partnership with the Ministry of Health of the Republic of Karakalpak since 2002, and has developed a Comprehensive Care for All strategy that has ambulatory care from day one at its core. This model was formally accepted as a model of care for the Republic of Karakalpak in 2011.[40]

In South Africa, the cost of MDR-TB treatment accounts for close to 55% of the total TB budget.[37] MSF, in partnership with the City of Cape Town and the Provincial Government of Western Cape, has developed a patient-centred, decentralised model of care whereby patients initiate treatment in their local clinic, with hospitalisation only when clinically indicated. This model has since been adopted by the provincial Department of Health in other sub-districts in the Western Cape. In 2013, 79% of DR-TB patients starting treatment in Khayelitsha did so in primary care facilities within their community, and a further 15% started in a local district hospital with discharge back to primary care shortly thereafter; only 6% required admission to the specialist TB hospital for treatment initiation.

GRAPH 1: DISAGGREGATED COSTS OF CARE IN DECENTRALISED AND DECENTRALISED MODELS[41]



Since introducing decentralisation of DR-TB care and improved access to rapid diagnostics (LPA and Xpert MTB/RIF) in Khayelitsha, time from sputum sampling to treatment initiation has decreased from 73 days in 2007 to seven days in 2013.[20] Treatment success rates remain comparable to the rest of South Africa. Decentralisation of care has led to a threefold increase in case detection since 2007, and more than 90% of diagnosed cases are started on treatment (compared to 42% of detected MDR-TB cases started on treatment nationally), potentially reducing DR-TB transmission within the community.

A study in the same region in South Africa found that the fully decentralised model in Khayelitsha was 42% cheaper than a projected fully centralised hospital-based model, saving over $2,000 per patient per treatment course.[41] The study projected that the potential annual cost-savings to the national TB programme – with full implementation of decentralised DR-TB care across South Africa – could reach up to R847 million (approximately $79.5 million). However, nearly three years after the Department of Health adopted a national DR-TB decentralisation policy, progress has been slow and uneven in many areas in South Africa.

Full decentralisation of TB care requires the decentralisation of TB diagnosis and treatment to happen in parallel. Development of diagnostic assays for rapid detection of drug resistance that are suitable for implementation at district level and below would be pivotal to support the implementation of decentralised DR-TB care.

Continued overleaf ⋯

Improving treatment outcomes continued

BOX 2: NEGLECTED NEEDS: DIAGNOSING AND TREATING CHILDREN

WHO recommendations on using Xpert MTB/RIF to diagnose paediatric TB have been rapidly included and all countries have a recommendation regarding Xpert MTB/RIF and children included in national guidelines (except Zimbabwe, but the use occurs in practise).[m] Although country uptake of the latest WHO recommendations for use of Xpert MTB/RIF for paediatric TB diagnosis appears strong, implementation of procedures for collection of alternative respiratory and non-respiratory sample types lags behind. In Kenya, Myanmar and Zimbabwe, use of Xpert MTB/RIF for paediatric TB diagnosis is limited to sputum and induced sputum samples. Country guidance supporting the use of respiratory and non-respiratory samples for paediatric diagnosis with Xpert MTB/RIF is critical to improve the difficult process of collecting adequate diagnostic samples for young children.[42]

Although today's paediatric fixed-dose combinations (FDCs) do not meet WHO-recommended dosages,[43] they remain recommended over mono-substance tablets for treating children.[44] FDCs are easier to administer, decrease the pill burden and improve adherence, increasing the chance for successful treatment completion.[45]

Nonetheless, in five out of eight surveyed countries, DS-TB can still be treated with mono-substance formulations per national guidelines. Paediatric FDCs are the main recommended treatment nationally only in South Africa and Zimbabwe. Brazil and India – where children under 15 accounted for 3% and 7% of all new TB case notifications in 2012, respectively[2] – still only recommend mono-substances in their national guidelines.

All countries have a section in their national MDR-TB guidelines dedicated to the treatment of MDR-TB in children. In countries for which data were obtained, the numbers of children on MDR-TB treatment were small despite the proportion of paediatric cases with drug resistance being similar to the proportion in adults globally.[46, 47] Despite the challenges, children generally do well on MDR-TB treatment[48] and greater efforts should be made to look for, diagnose and start children on MDR-TB treatment. Bacterial confirmation should be sought, but it should not delay treatment initiation.

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m. Refer to full survey of results online: msfaccess.org/outofstep

ENSURING AVAILABILITY AND AFFORDABILITY OF TB MEDICINES: ADOPTION, HARMONISATION, REGULATION

In order to ensure patients have access to quality-assured TB and DR-TB medicines, countries must take steps to ensure medicine availability, affordability and adoption in guidelines and programmes.[49] Adoption includes implementation of appropriate national pharmacy policies, including national essential medicines lists (EML) and standard treatment guidelines (STGs), that are compliant with the most updated WHO recommendations for TB care.

Up-to-date guidelines enable rational prescribing patterns by physicians that can reduce the development of drug resistance and help prepare countries for the introduction of new tools and treatments. They also provide clear information to manufacturers on which medicines should be registered and marketed in these countries.

The STG and EML of each country were reviewed for inclusion of key TB medicines. All national TB treatment guidelines, STGs and EMLs should be updated regularly to include all necessary TB treatments. Not doing so may hinder national TB programmes' ability to procure needed drugs and reduce or block the availability of these treatments for use in patients with TB.

This section looks at key indicators on market regulation, quality assurance and adoption of key medicines in addition to country readiness to scale up access to Group 5 and new medicines.

MSF's survey found that:

- In four countries, fixed-dose combinations (FDCs) for DS-TB are available in the private sector;
- Quality criteria varied by country and by procurement mechanism and was not always aligned with WHO quality criteria standards;
- No national EML listed all DR-TB drugs with TB indications;
- No national treatment guidelines included all Group 5 medicines; and
- Four countries had practicalities in place for access to new treatments under compassionate use or similar programs, but only two countries had processes to rapidly register new treatments.

MEDICINES FOR DS-TB

Ensuring access to appropriate treatment for drug-sensitive (DS-TB) is one of the key measures that can help stop further generation of drug resistance. All patients should ideally be treated with FDCs as they facilitate rational prescribing and treatment adherence, increasing the likelihood of successful treatment outcomes.

In seven out of the eight surveyed countries (all but India), adult FDCs for DS-TB are on the national EML; however, they are only referred to in the STGs of six countries **[see page 14 for paediatric FDCs]**.

Without FDCs on the STG for India and the Russian Federation, challenges remain for the full adoption of FDCs as a standardised treatment for DS-TB.

MARKET REGULATION

In most surveyed countries, both adult and paediatric FDCs for DS-TB are available in the public sector, and in half of surveyed countries these FDCs are also available in the private sector. India is the only exception where FDCs are not available for DS-TB. Medical practices in the private sector are not systematically aligned with national guidelines.

Where the private sector is not properly regulated, there is a risk of irrational prescriptions, which is a major factor fuelling drug resistance. For example, mono-substance formulations may be dispensed in the private sector, even when only FDCs are recommended nationally for DS-TB.

In Brazil and Zimbabwe, TB medicines are not available in the private sector, except for those with non-TB indications such as fluoroquinolones or some Group 5 medicines. In contrast, in at least four of the eight countries (India, Myanmar, Russian Federation, and Uzbekistan), the majority of TB medicines are available in the private sector. In Myanmar and the Russian Federation, these medicines are available without systematic prescriptions, increasing the risk of misuse.

Continued overleaf

Ensuring availability and affordability of TB medicines continued

BOX 3: COMPASSIONATE USE: AN IMPORTANT INTERIM SOLUTION[o]

Compassionate use (CU) is a life-saving tool to enable patients without other treatment options to get early access to new drugs.

With two new TB drugs becoming available, MSF has been using CU and similar programmes to offer new drugs to patients within individually-tailored regimens for XDR-TB or for whom standard MDR-TB regimens are inadequate. National regulatory processes that allow the use of investigational new drugs in patients must be in place in order to do so.

MSF has had an agreement with licence-holder Janssen since 2012 that grants access to bedaquiline to MSF-supported projects in countries where national CU frameworks are in place. In 2013, MSF worked with the Armenian NTP, through a CU programme, to start the first MSF patient on bedaquiline. MSF recently established an agreement with Otsuka, the licence holder of delamanid, to enable selected MSF-supported projects to access the drug in a CU framework.

As of September 2014, 51 MSF patients in three countries (Armenia, Kenya, and Russian Federation) have received bedaquiline through compassionate use. MSF has not yet been able to prescribe delamanid to patients. MSF's longest running CU programme is in Armenia, where MSF worked with the national TB programme to establish the national CU framework that has enabled the use of bedaquiline for 47 patients as of 1 September, 2014. Although the results from patients completing the full two-year treatment course are not available yet, early results from Armenia show culture conversion at two months was achieved by 55% (11/20) of patients, and at six months by 88% (15/17) of patients.[56]

In 2013, MSF in Khayelitsha, South Africa, was approved as a site for the national clinical access programme and started accessing bedaquiline for patients with pre-XDR and XDR-TB in April 2013. To date, 22 patients have commenced bedaquiline-containing regimens at this site (one of six sites currently actively enrolling patients onto the programme across South Africa).

It is also important to ensure access to the accompanying drugs needed to build a treatment regimen for patients accessing the new TB drugs through CU programmes. These are usually Group 5 drugs, but there are often additional access barriers to accessing these drugs in countries using the CU framework. When considering CU access, the availability of Group 5 medicines such as linezolid, clofazimine and imipenem needs to be included in national-level discussions from the beginning, to ensure importation waivers are obtained for these drugs. Registration and adoption of Group 5 medicines at the national level is a challenge, and the process takes time **[see page 17]**. Overcoming these barriers to access requires political will at the national level.


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o. Compassionate use is 'the use of an investigational drug outside of a clinical trial by patients with serious or life-threatening conditions who do not meet the enrolment criteria for the clinical trials in progress.' Compassionate use programs and other national regulatory processes, such as South Africa's clinical access programme, allow the use of investigational new drugs in patients. For more information, see MSF's report DR-TB Drugs Under the Microscope.

In India, the Drug Technical Advisory Board recommended that 35 antibiotics, including a series of TB medicines, be included in the revised Schedule H1. These medicines will be scrutinised to find out how they are sold and used, in an effort to prevent them from being dispensed indiscriminately and contributing to the development of drug resistance.[50] Initiatives such as this are welcome and if successful will contribute to more stringent market regulation in the private sector. However, the implementation is very weak and still does not regulate TB prescriptions in a systematic manner.

QUALITY ASSURANCE

The source of funding for TB drugs and the procedure for countries to purchase them has a direct impact on their quality, particularly considering the varying stringency of national medicine regulatory authorities (NMRA) across countries. Quality criteria differ depending on whether the purchases are covered by domestic funding or external donors such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), who link their grants to the supply of quality-assured medicines. Furthermore, even within countries there is often no harmonisation of quality criteria set by the different purchasing and mixed funding mechanisms for DS-TB and DR-TB.

In the eight surveyed countries, the procurement of DS-TB and DR-TB medicines does not appear to be systematically linked to selection criteria compliant with WHO quality standards. However, Brazil and Myanmar have recognised the negative impact of the use of non-quality-assured TB medicines, and increasingly rely upon WHO quality standards for procurement, even though quality-assured TB drugs are more expensive.

BOX 4: FIGHTING FOR ACCESS TO LOW-COST GENERIC LINEZOLID IN SOUTH AFRICA

In June 2014 MSF received approval from the South African Medicines Control Council (MCC) to import a dramatically more affordable version of a Group 5 drug, linezolid, in order to provide better treatment options to patients with DR-TB in Khayelitsha, Western Cape. Linezolid is one drug in an already expensive regimen for pre-XDR and XDR-TB; with the brand name product costing $65 per pill, linezolid costs $49,000 per patient in South Africa for the two-year treatment period. By contrast, MSF can now import the quality-assured generic version (approved by UK regulatory authorities) for 88% less at $8 per tablet.

"It took three years for MSF to find a solution for accessing more affordable linezolid in South Africa. We unsuccessfully tried asking for a lower price for the brand name drug; even the process of getting the import waiver from the MCC took over six months. The high price of the brand name product was consuming up to 10% of the entire annual budget for MSF's HIV and TB project operations in Khayelitsha, which limited the number of patients to whom we could offer linezolid," says MSF TB Doctor, Jennifer Hughes.

MSF is now the only entity allowed to import the generic product into South Africa after applying for permission from the MCC under section 21 of the Medicines and Related Substances Control Act.[55] The MCC is reviewing generic linezolid for full registration in South Africa through a fast-track registration process and is supposed to provide a decision on market authorisation for priority medicines after a nine–month assessment. However, the current evaluation was started in June 2013 and remains under assessment at the time of publication. Full registration of a quality-assured generic linezolid product by the MCC would allow the more affordable version to be procured nationally for provision through the public sector, expanding access to hundreds, if not thousands, of DR-TB patients in South Africa.

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ADOPTION OF WHO-RECOMMENDED MEDICINES

None of the eight surveyed countries have national treatment guidelines and EMLs that are fully consistent with current WHO recommendations. In only two countries (Brazil and South Africa) had the national EMLs been updated in the last 12 months. In the majority of the countries surveyed, the national EMLs were updated more than three years ago, and are out of date compared to the WHO EML revision cycle of every two years.[51] This is particularly problematic for DR-TB medicines. None of the EMLs of surveyed countries included all DR-TB medicines with TB indications (i.e. from groups 2,3,4 and 5). Group 5 medicines included in national EML without a TB indication create potential country procurement issues.

COUNTRY PREPAREDNESS TO SCALE UP MDR-TB AND XDR-TB TREATMENT

The adoption of Group 5 medicines for third-line or XDR-TB therapy, including the repurposed drugs clofazimine, linezolid and imipenem/cilastatin, in national policies is an important pre-condition to providing adequate MDR-TB and XDR-TB care. However, none of the eight countries surveyed have all of the Group 5 medicines in the national treatment guidelines. India has included all of them in the 2014 Standards of Care in India, but these are not guidelines,[52] so it remains to be seen if this will translate into an updated STG and national EML.

The absence of these medicines in national treatment guidelines means it may be difficult to use them as a standard treatment for MDR-TB or XDR-TB. This situation can also deter manufacturers from registering these

BOX 5: MSF AND SHORTENED MDR-TB TREATMENT REGIMENS

Currently a multinational randomised controlled trial (known as the STREAM trial) is investigating the safety and efficacy of a nine-month treatment course for MDR-TB.[p,57] Multiple countries are using this shortened regimen as part of operational research (OR). MSF is trialling this regimen as part of OR in Uzbekistan and Swaziland that represent a range of epidemiological challenges, and, with other non-MSF cohorts, will contribute additional information on the potential use of this shortened regimen. MSF also uses the shortened regimen in clinical projects (non-OR projects) in conflict settings and other unstable contexts where it is not possible to safely and confidently start the current WHO-recommended two-year regimen.

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In Uzbekistan, operational research conducted by MSF and the MOH using the nine-month MDR-TB regimen started in 2014. Seventy-five patients have started on this shortened treatment (as of August 2014) and so far 10 patients have completed treatment with negative sputum cultures, and are being monitored for relapse. Although this regimen still contains an injectable and six oral drugs, if it is shown to be equivalent to the current two-year regimen, it offers a number of advantages to both patients and programmes as an interim solution until new, more tolerable and effective treatment regimens are available.

p. The regimen, sometimes referred to as the "Bangladesh" or "STREAM" regimen, consists of moxifloxacin (replaced gatiflozacin), clofazimine, ethambutol and pyrazinamide given for 40 weeks, supplemented by kanamycin, isoniazid and prothionamide in the 16 weeks of the intensive phase. All drugs are given daily except for kanamycin which is given thrice weekly after 12 weeks.

medicines in the countries and lead to more complex import procedures. Thus the current lack of consistency between the national EML and treatment guidelines hinders scaling up the use of the Group 5 drugs, and will likely impact the timely introduction of the new anti-TB drugs bedaquiline and delamanid.

Compassionate use (CU) programmes have been recommended by WHO since 2008 to provide early access to new treatments for TB and other diseases.[53, 54] Four out of the eight surveyed countries (Brazil, Russian Federation, South Africa and Zimbabwe) have a legal framework for CU in place or have set-up practicalities to allow access to investigational medicines.

On the legal side, Indian law[n] allows the import of an unregistered medicine on a named-patient basis for an unmet medical need, and this allows patients to obtain import permits for new TB drugs which may have been provided by companies under compassionate use programmes or procured from other countries where the drug is already registered. Kenya does not have compassionate use legislation or equivalent regulations in place but arrangements have been made to enable the use of new TB drugs in patient name-based programmes.

Medicines obtained through CU can only be offered to a restricted group of patients. Regulatory strategies allowing broader national access to new TB medicines should also be considered, such as fast track registration. In South Africa and Zimbabwe, rapid registration processes are already legally available. However, the existence of rapid registration processes does not guarantee their use, nor do they necessarily eliminate delays in product registration when employed **[see page 17]**.

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n. Indian Drugs and Cosmetic Rules, Rule 36 states: 'Small quantities of drugs, the import of which is otherwise prohibited under section 10 of the Act, may be imported for personal use…' Available from: http://ptlb.in/ecommerce/wp-content/uploads/2014/03/Drugs-And-Cosmetics-Rules-1945-Of-India.pdf

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CHALLENGES IN ACCESSING NEW AND REPURPOSED TB DRUGS

New and repurposed drugs show promise in clinical studies, but access barriers stand in the way of these important therapies getting to patients who need them as part of more robust and effective regimens. Even if countries implement enabling pharmaceutical policies to facilitate adoption of new drugs and diagnostics, old access challenges still need to be addressed. Urgent action is needed to address critical issues including high price, lack of registration and data gaps in how to best and most safely use these new drugs.

The table below details each of these drugs, their challenges, and how to address these challenges.

Drug	Manufacturer / Developer	Development stage	Access barriers	What needs to happen
Bedaquiline (Bdq)	Janssen	• Accelerated approval from U.S. Food and Drug Administration (FDA), conditional approval from European Medicines Agency (EMA), full approval in the Russian Federation, all based on phase IIb data. Approved by the Ministry of Food and Drug Safety (MFDS) in South Korea in March, 2014. • Phase III in planning. • Recommended by WHO for use in DR-TB patients with no other treatment options.	• Price (see page 24). • Intellectual property barriers (compound and multiple secondary patents) until 2029 that limit generic competition or development of fixed-dose combinations. • Delays in registration with multiple NMRAs. • Little data on use with other new TB drugs (e.g. delamanid). • Not yet included in the WHO EML.	• Access to a more affordable price, especially for middle-income countries (MICs). No low-income country or MIC should pay more than $900 for a 6-month course. • Reduction of intellectual property barriers through use of TRIPS flexibilities or voluntary licensing. • High burden TB countries' NMRAs must prioritise registration. • Inclusion on the WHO EML. • Rapidly commence trials looking at combining Bdq with other new drugs and in shorter regimens.
Delamanid (Del)	Otsuka	• Full approval by EMA, Pharmaceutical and Medical Devices Agency in Japan (PMDA), based on phase IIb data. • Phase III completed enrolment. • WHO recommendations under development.	• Global price strategy is not yet known. The price for a 6-month course is US$28,000 in the UK and $40,000 in Japan. • Only currently registered in the European Union and Japan. • Intellectual property barriers (compound and secondary patents) until 2031 that limit generic competition or development of fixed-dose combinations. • No proactive plans to register in high-burden TB countries or trial countries. • Little data in use with other new TB drugs (e.g. bedaquiline). • Not yet included in the WHO EML.	• Pricing for L&MICs must be affordable and enable access. • Reduction of intellectual property barriers through use of TRIPS flexibilities or through voluntary licensing. • Otsuka must urgently register this medicine in high-burden TB countries and trial countries; in the meantime, delamanid should be accessible through CU programmes. • Increased transparency from manufacturer on price and registration questions. • Inclusion on the WHO EML once WHO recommendations made. • Rapidly commence trials looking at combining delamanid with other new drugs and in shorter regimens.

Drug	Manufacturer / Developer	Development stage	Access barriers	What needs to happen
PA824	TB Alliance	⇢ In Phase II development. ⇢ Phase III trial planned (STAND-TB).	⇢ As it will not be registered as a single drug, important it is made available for development of drug combinations beyond those currently being trialled. ⇢ No plans for CU.	⇢ Review possibility of allowing access to PA824 for CU as soon as Phase II trials are successfully completed. ⇢ Allow access to PA824 for use in trials combining it with other new drugs and additional shorter regimen trials.
Clofazimine	Novartis	⇢ Registered for use in treating leprosy. ⇢ Recommended by WHO as a Group 5 drug for TB treatment.	⇢ Does not have an indication for TB. ⇢ Only one quality-assured manufacturer makes this drug and quantities may not be sufficient for scale up of clofazimine-containing regimens, including new shortened regimens. ⇢ Not yet included in the WHO EML for TB.	⇢ Novartis should rapidly pursue obtaining a TB indication for clofazimine. ⇢ Tech transfer for API production to allow sustained availability; prioritise reformulation to a presentation more suited to hot and humid environments, and allowing dosing adaptation. ⇢ Current and future generic manufacturers of active pharmaceutical ingredient and finished product of clofazimine should pursue WHO prequalification. ⇢ Inclusion on the WHO EML for TB.
Linezolid	Pfizer, Hetero	⇢ Registered for use in treating resistant infections caused by typical bacteria. ⇢ Recommended by WHO as a Group 5 drug for TB treatment.	⇢ Does not have an indication for TB. ⇢ Intellectual property barriers (secondary patents) that could preclude importation of low-cost generics until 2021 in some countries. ⇢ Despite the entry of one generic manufacturer (Hetero), price remains an issue. ⇢ Not yet included in the WHO EML for TB.	⇢ Pfizer or Hetero should register linezolid in all high burden TB countries as a priority. ⇢ Pfizer and Hetero should pursue a TB indication for this drug. ⇢ Price reductions to improve affordability. ⇢ Use of TRIPS flexibilities, if needed, to remove remaining secondary patents in countries where treatment scale up is needed. ⇢ Inclusion on the WHO EML for TB.

ENSURING SUFFICIENT RESOURCES: STEPPING UP DOMESTIC AND INTERNATIONAL FUNDING

While the new global TB strategy is a positive display of political commitment, action and funding must follow to strengthen TB and DR-TB programmes, close life-threatening gaps in access to proper diagnosis and treatment, and meet global 20-year targets.

CURRENT GLOBAL FUNDING

Globally, current funding levels to combat TB do not meet the necessary levels. According to the Stop TB Partnership, at least $8 billion is needed annually by 2015 for low- and middle-income countries to meet the objectives laid out in the Global Plan to Stop TB (2011 – 2015) for programmatic implementation and research and development.[2] The vast majority of TB funds available in 2013 for low- and middle-income countries outside of the European region ($5.3 billion) came from domestic sources, but only amounted to 67% of the annual amount needed by 2015 according to WHO. In addition, international funds amounted to only half of the total needed by 2015.[2]


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CURRENT NATIONAL FUNDING

All surveyed countries have significant TB disease burdens and require sufficient resources to properly respond to the national public health needs. In reality, the low-income countries (LICs) surveyed (Kenya, Myanmar and Zimbabwe) had the greatest funding gaps, between 57–61%. India, Russian Federation, and South Africa had the largest budgets. Brazil, Russian Federation and South Africa relied the least on international funding, with 95% or more of TB funding sourced domestically. India lagged behind these countries with 57% of TB funding sourced domestically.

STEPPING-UP FUNDING

Political will, action and funding are not keeping pace with the epidemic or with the international community's stated commitment to support the fight against TB and DR-TB. There is not enough financial support for diagnosis, treatment or drug development.

National TB Programme (NTP) budgets, currently monitored to indicate sufficiency of TB response, are not a complete picture of need, and a stronger, standardised surveillance mechanism for TB funding requirements and MDR-TB funding allocations is needed. In most countries, funding needed for inpatient and outpatient TB care (e.g., staff, infrastructure, hospital admissions, outpatient visits, etc.) is not reflected in the NTP budget. In some cases, however, for example the Russian Federation, this funding is accounted for because care is carried out in TB-specific hospitals and clinics.

Overall, heightened support is needed for high-burden countries, including low- and middle-income countries, based on a comprehensive understanding of country needs.

BOX 6: SPOTLIGHT ON THE GLOBAL FUND

The Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), followed by USAID, is the largest international funder for TB. The Global Fund estimates a total of $14.5 billion is needed for TB care and control for Global Fund-eligible countries between 2014–2016.[q,59] Of this amount, the Global Fund expects $9.7 billion to come from domestic sources, $0.6 million from non-Global Fund donors, and $4.3 billion ($1.4 billion a year) from the Global Fund for 2014–2016 (Fourth Replenishment Period).[60]

Although the Global Fund has been a lifeline for TB, as well as HIV and malaria programmes, it has been unable to raise the level of donor contributions needed to meet its funding targets. A total of $12.2 billion pledged to the Global Fund for the Fourth Replenishment Period for HIV, TB, and malaria as of December 2013, the largest amount pledged in Global Fund history.[61] Of these funds, 18%, or $2.2 billion, will be allocated towards TB for 2014–2016, only half of Global Fund's $4.3 billion ask.[62] Global Fund donor countries will likely be asked to contribute again during the Fourth Replenishment Period Mid-term Review. If this effort fails again, the largest donor of global TB and DR-TB programmes support will remain severely under-funded, limiting the number of people who can be reached with quality TB and DR-TB services.

Global Fund support is further hampered by changes in the new funding model being rolled out and confusion among countries that the grant amounts they are allocated at the start of this process represents a funding ceiling for domestic TB programmes. In actuality, country concept notes and proposals to the Global Fund need to reflect full needs to combat TB and DR-TB, including the funding to cover the provision of new tools (especially for drugs and diagnostics).

The Global Fund Secretariat and Board of Directors need to raise funds to close the funding gap. In addition, the Mid-term Review estimates must take into account the funding needed for the procurement of the new TB drugs emerging from the pipeline.

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q. This includes US $1.9 billion a year for scale-up of rapid molecular diagnostics and associated laboratory strengthening, along with US $2.6 billion a year for the treatment of DR-TB.

Continued overleaf ⋯

Ensuring sufficient resources continued

BOX 7: SPOTLIGHT ON ACCESS TO BEDAQUILINE

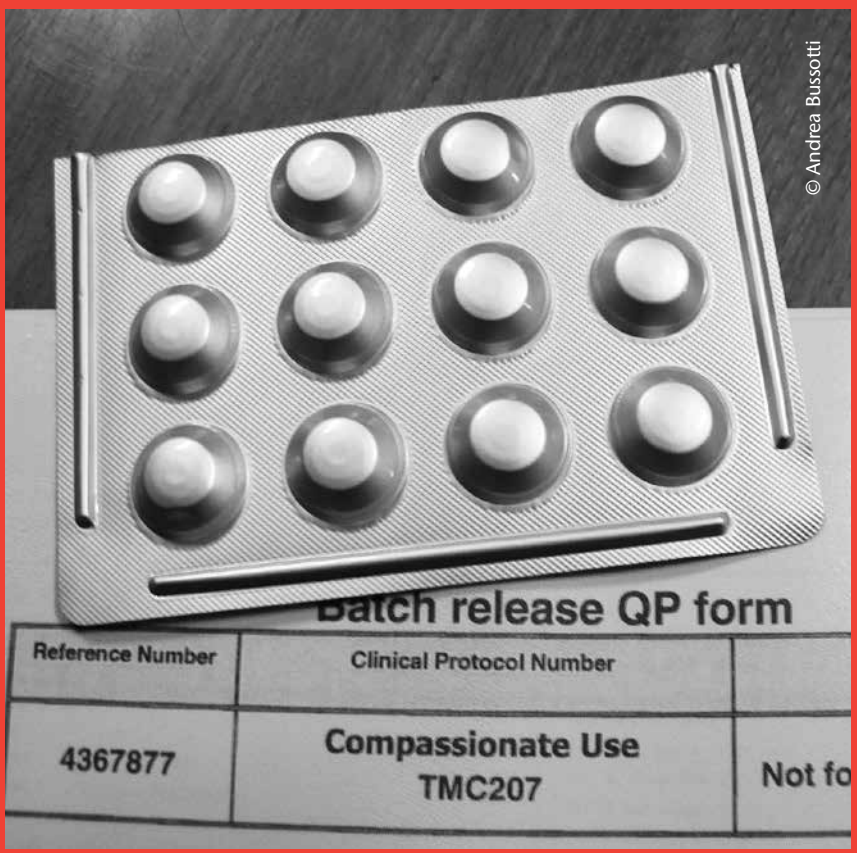
One of the first new drugs approved to treat TB in 50 years, bedaquiline, was given accelerated approval by the US Food and Drug Administration (FDA) at the end of 2012 for treatment of MDR-TB in cases where other treatment options have failed. Despite the need for TB medicines to be administered in combinations of at least three drugs, bedaquiline was developed as a single drug – on top of the standard WHO regimen, which is poorly tolerated – all the way up to market approval. Although research into how bedaquiline should be used with other drugs as part of a new regimen is now beginning, it will take many more years before this research can be translated into treatment guidelines and new regimens that can be routinely used in treatment programmes.

While bedaquiline is potentially a necessary drug for many MDR-TB patients, it remains largely out of reach. In the majority of high burden countries, bedaquiline has only been used as part of compassionate use programmes **[see page 16]**. National regulatory processes are mandatory safeguards for public health, but flexibilities should be included in such systems to allow access without other treatment options. Considering the lack of therapeutic alternatives, interim approvals should be considered by countries on the basis of existing clinical data and registration status at stringent regulatory authorities.

Although in-country registration must be prioritised, price is also a barrier. Janssen, the company holding the intellectual property rights to bedaquiline, has priced a six-month course at $3,000 and $900 for middle- and low-income countries, respectively. For drugs like bedaquiline, where public funding has contributed to drug research and development, and there have been financial benefits such as the FDA priority review voucher, as with bedaquiline, there should be transparency in how these contributions are reflected in the price. Pricing strategies should also take into account public health priorities, endemic country public health budgets, and efficient use of public funding towards drug purchases through, for example, the Global Fund.

The cost of each TB drug needs to be considered in the context of its contribution to the total cost of the regimen. TB programs are already struggling to scale-up access to today's $1,500–$3,000 MDR-TB regimens. As more evidence of bedaquiline's efficacy in combination with other drugs becomes available through clinical research, countries may face tough financial choices in trying to provide the newer, more effective treatment regimens to patients in need. These financial choices affect middle-income countries in particular, who shoulder the bulk of the global TB burden, but often have severely underfunded TB budgets and therefore are disproportionally affected by high drug prices. Janssen should make all efforts to make bedaquiline more accessible by immediately dropping the middle tier of its pricing strategy and offering all middle- and low-income countries the same lowest price.

The global pricing strategy of Otsuka for its newly registered drug delamanid is unknown but it is hoped that the company does not replicate the tiered pricing for middle-income countries and ensures its pricing structure is affordable and transparent. Almost one year after its conditional approval by EMA, delamanid is still not registered in any high-burden country.



BOX 8: ENSURING A HEALTHY PIPELINE: RETHINKING TB DRUG RESEARCH AND DEVELOPMENT

The challenges of current MDR-TB treatments are well documented:[35] there is an urgent need for shorter regimens that contain multiple novel and better tolerated drugs. In order to develop new treatment combinations to stay ahead of the antibiotic resistance, it is vital that there is a healthy TB drug pipeline with a number of compounds in all phases of development. However, currently there are no compounds in Phase I clinical development.[63] Research and development (R&D) of TB drugs suffers from significant weaknesses throughout all stages of development, hampering the development of new regimens.

The way TB drug research is done today is not adequately responding to the needs of patients and TB programmes. With chronic under-funding and major pharmaceutical companies withdrawing or reducing their investment in TB research and development, novel approaches must be considered to re-energise the pipeline, bring new funders to the arena, prioritise regimen development early in the drug development process, and ensure access and affordability for products.

PUSH, PULL AND POOL: ACCELERATING INNOVATION AND ACCESS FOR NEW TREATMENT REGIMENS FOR TB WITH MSF'S '3P PROPOSAL'

MSF, in collaboration with other partners, has developed a proposal for an alternative way to conduct research and development for TB regimens that addresses some of the shortcomings of the current drug development landscape. The aim is to ensure a steady supply of new TB drugs for regimen development. The '3P Project'[64] aims to create a new open collaborative framework for regimen development by implementing push, pull and pool incentive mechanisms to facilitate the necessary and appropriate R&D for TB medicines:

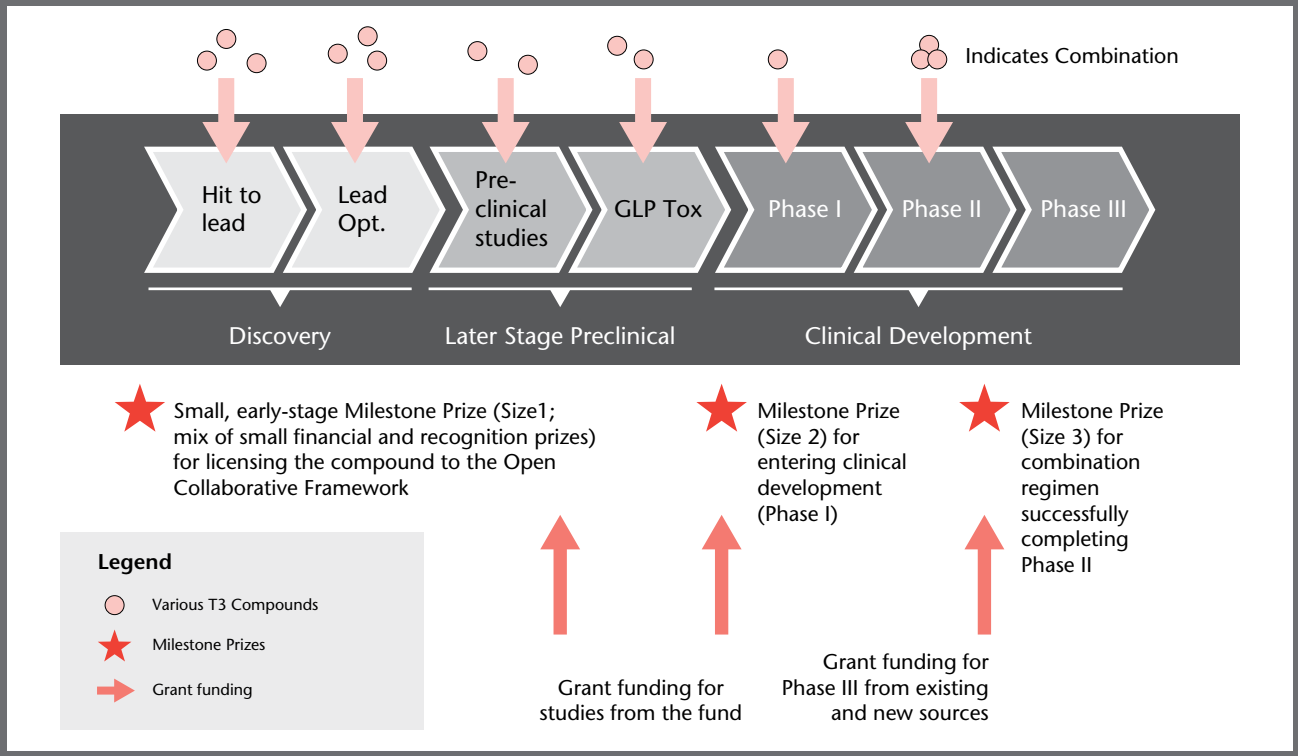
Push funding to finance R&D activities upfront (i.e. through grants);

Pull funding to incentivise R&D activities through the promise of financial rewards on the achievement of certain R&D objectives (i.e. through milestone prizes);

Pooling of data and intellectual property to ensure open collaborative research and to ensure fair licensing for competitive production of the final products.

These well-targeted incentives aim to bring new researchers and developers to the problem, re-engage traditional investors in TB drug development, ensure a healthy drug development pipeline, and ensure that several drug candidates are developed in parallel as combination regimens.

For more information visit: http://www.msfaccess.org/push-pull-pool



CONCLUSIONS AND RECOMMENDATIONS

With a confluence of changes affecting both the TB epidemic and the global response to it, now is the time to capitalise on international consensus around more ambitious post-2015 targets and innovative thinking about the future of the global TB response, including more effective and easier to use diagnostic and treatment approaches. Each country in this survey has different strengths and areas for improvement, and countries, implementers and donors must consider how to build on the strengths and address gaps on a country-by-country basis. TB-endemic countries, WHO, manufacturers, donors and treatment providers must work together to close the deadly gaps in diagnosis and treatment of people with TB. All countries should be able to implement and utilise proven and innovative tools, guidelines and policies to step up and more effectively address the TB and DR-TB epidemics.

TB-ENDEMIC COUNTRIES

Strengthening laboratory capacity:

- Strengthen national laboratory capacity for culture and DST to meet diagnostic and treatment monitoring needs;
- Invest into timely uptake and roll-out of new technologies for TB diagnosis, according to WHO recommendations;
- Support use of rapid diagnostics for detection of TB and drug resistance at decentralised sites;
- Invest in improving laboratory quality through full enrolment in external quality assurance (EQA) programmes and by increasing the number of laboratories which have an accredited quality management system in place; and
- Ensure scale-up of Xpert MTB/RIF is matched with adequate laboratory capacity for culture and microscopy to ensure treatment monitoring, and DST tests to detect resistance to drugs other than rifampicin.

Access to proper diagnostic work-ups:

- Improve access to laboratory-confirmed diagnosis and DST in order to meet Global Plan to Stop TB (2011–2015) targets;
- Strengthen implementation of procedures for collection of alternative respiratory and non-respiratory sample types for paediatric TB diagnoses;
- Fully implement active case finding and contact tracing strategies to help reduce millions of missed TB diagnoses;
- Ensure DST for all retreatment cases, in order to ensure the correct treatment is commenced at initiation, and avoid use of Category 2 treatment; when DST is not available, empirical MDR-TB treatment can be considered while awaiting DST in high MDR-TB burden areas.

Models of care:

- Monitor treatment gaps, in particular for MDR-TB;
- Remove the need for compulsory hospitalisation for TB patients, both DR-TB and DS-TB, particularly for extended periods of time;
- Promote a standard of care for TB with daily dosing of TB medicines in FDCs, including for children.

Rational use of medicines:

- Implement WHO recommendations for treatment of MDR-TB and XDR-TB by adapting national guidelines;
- Adopt and promote the use of FDCs in adults and children, in public and private sectors, by including FDCs in national guidelines, as well as in national EML in order to reduce the use of mono-substance formulations for DS-TB treatment in adults and children;
- Align medical practices in the private sector with national guidelines for DS-TB, MDR-TB and XDR-TB;
- Strengthen market regulation to enforce the rational use of TB medicines in public and private sectors to preserve efficacy of DS-TB and DR-TB medicines;
- Ensure procurement and use of quality-assured (including WHO prequalified) TB drugs;
- Ensure that national TB treatment guidelines and EML are in line with WHO guidance for DR-TB and include necessary group 2,3,4 and 5 drugs;
- Promote capacity of national medicine regulatory agencies (NMRA) so that they are able to assess quality when it comes to production, importation and wholesaling of TB medicines.

Preparation for scale-up of new treatments:

- Ensure that there is regular review and updates of national TB treatment guidelines, STG and EML, and that they correspond to the most recent WHO guidance: inclusion of Group 5 medicines in national guidelines and EML in line with WHO recommendations is a priority;
- Put in place procedures that allow importation and dispensation of quality-assured Group 5 medicines not yet registered;
- Countries should implement the necessary legislation for CU as soon as possible. There should be parallel efforts to register new drugs so that they are available to more patients and a sustainable supply can be set up;
- Proactively reach out to manufacturers producing quality-assured products to ensure registration of their Group 5 medicines;
- Enable fast track registration procedures of priority TB medicines;
- Make use of international regulatory flexibilities, such as the collaborative registration process at the WHO prequalification programme, and recognise market authorisations granted by stringent NMRAs for priority medicines.

Long-term solutions:

- National programmes should ensure transparency and ease in obtaining data to analyse TB programmes;
- Support the creation of the 3Ps Project **[see page 25]** financially and politically to ensure a healthy drug development pipeline and the development of new treatment combinations to effectively, safely, quickly, affordably and simply treat all forms of TB;
- Reform or maintain patent laws to take full advantage of legal flexibilities under international trade agreements, to ensure that intellectual property barriers do not hinder access to TB medicines or the development of new regimens.

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Continued overleaf


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WORLD HEALTH ORGANIZATION

Strengthen laboratory capacity:

- Continue delivering necessary documentations and training material to support and guide endemic countries' activities towards strengthening of national laboratory networks and implementation of quality assurance programmes and quality management systems;
- Strengthen the supranational laboratory network for EQA.

Introduction of new diagnostic technologies:

- Continue issuing timely guidance and recommendations to support roll-out of new technologies.

Promote decentralised models of care:

- Promote decentralised, patient-centred models of care and investigate the feasibility of decentralising treatment initiation to bring both diagnosis and treatment closer to the patient.

Promote rational use of medicines:

- Promote the use of FDCs for DS-TB at country level and provide technical support for the adaptation of national guidelines for MDR-TB and XDR-TB;
- Promote the use of medicines compliant with WHO quality standards at country level;
- Provide practical guidance on the treatment of XDR-TB with new and repurposed drugs.

Prepare for scale-up of new treatments:

- Ensure all MDR-TB medicines, including new compounds, are added onto WHO EML and the Expression of Interest of WHO Prequalification Programme;
- Issue in a timely manner interim guidance for new compounds and update accordingly final treatment guidelines;
- Give guidance to countries on initiating a CU programme, facilitating fast track registration of the new compounds and introducing new regimens;
- Support countries in their use of the collaborative registration process at WHO prequalification programme and make attempts to expand this process to stringent NMRAs;
- Support the creation of a system of consolidated pharmacovigilance data to ensure the collection of robust safety data on new drugs and new regimens.

Consider long-term solutions:

- Support the creation of the 3Ps Project **[see page 25]** financially and politically to ensure a healthy drug development pipeline and the development of new treatment combinations to effectively, safely, quickly, affordably and simply treat all forms of TB.

MANUFACTURERS

[See pages 20–21 for manufacturer specific recommendations]

Prepare for scale-up of new treatments:

- Provide access to innovative TB medicines through CU;
- Proactively register new medicines in countries where clinical trials take place and other high-burden TB countries;
- Register quality-assured Group 5 medicines and new compounds, even in small markets;
- Ensure an affordable, transparent price for all DR-TB medicines for all low- and middle-income countries;
- Accelerate combined drug research to create appropriate regimens;
- Ensure that intellectual property barriers (patents and test data) do not preclude generic competition or development of appropriate FDCs or other formulations.

Introduce new diagnostic technologies:

- Develop diagnostic assays for rapid detection of drug resistance in decentralised settings, based on guidance provided by the consensus Target Product Profile (TPP); [65]
- Ensure adequate distribution networks and adherence to negotiated prices for products;
- Offer contracts that allow for reagent rental and flexible and transparent pricing structures for tests to allow for bundling or unbundling of maintenance contract costs, depending on country needs.

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DONORS:

- **Step up** political and financial support.

Prepare for scale-up of new treatments:

- Promote the exclusive use of quality-assured TB medicines at country level by harmonising quality criteria for TB procurement across donor procurement mechanisms.

Strengthen laboratory capacity:

- Fund strengthening of in-country laboratory networks and sample referral systems and support roll-out of WHO-approved TB diagnostic assays, including scale-up of Xpert MTB/RIF.

Support R&D:

- Fund independent clinical validation, demonstration studies and trials of new TB technologies.

Consider long-term solutions:

- Support the creation of the 3Ps Project **[see page 25]** to ensure a healthy drug development pipeline and the development of new treatment combinations to effectively, safely, quickly, affordably and simply treat all forms of TB.

ANNEX: ABRIDGED TABLE OF RESULTS

Key survey results discussed in this report are summarised here. Citations for the sources of all survey results, and the complete survey results, are available at: www.msfaccess.org/outofstep/

All currency in US dollars.

DIAGNOSTICS			
		Brazil	**India**
Brief Description of National Lab Network (public sector)	**Number of laboratories performing culture tests**	345 in 2013	51 in 2014
	Number of laboratories performing phenotypic 1st-line DST	39 in 2013	51 in 2014
	Number of laboratories performing 2nd-line DST	2 in 2014	7 in 2014
	Number of laboratories performing LPA	8 in 2012	45 in 2014
	Number of GeneXpert MTB/RIF devices in country	175 in 2013	89 sites in 2014[q]
For which patient groups do national guidelines recommend use of Xpert MTB/RIF?	**All presumptive TB cases**	Yes	No
	High-risk groups (persons at risk of HIV-associated TB and persons at risk of DR-TB)	Yes	Yes[e]
Which patient groups are systematically considered for 1st-line DST?		All new TB cases[h]	Previously treated patients, contacts of DR-TB patients, failures, TB/HIV coinfected patients, presumptive TB cases among PLHIV[r]
Estimation of access to proper diagnostic work-up for DS-TB and DR-TB detection	**% of TB cases with bacteriologically confirmed TB**	69.6% new cases, 69.2% relapse in 2014	64% in 2012
	% of bacteriologically confirmed TB cases with 1st-line DST results[b]	Unknown	Unknown[k]
	% of confirmed MDR cases with 2nd-line DST results[c]	12.3% in 2013	3.6% in 2012
Estimation of access to treatment for DS-TB and DR-TB?	**% of bacteriologically confirmed TB cases started on treatment**	100% in 2013	Unknown
	% of confirmed MDR-TB cases started on treatment	100% in 2013	85% in 2012
	% of XDR-TB cases started on treatment	100% in 2013	See footnote[o]
Cost of tests and reagents when purchased by NTP?	**Xpert MTB/RIF cartridge**	$9.98	Unknown

§BAL: broncheoalveolar lavage; CSF: cerebrospinal fluid; GA: gastric aspirate; GL: gastric lavage; IS: induced sputum; LNA: lymph node aspiration

a. Guidelines recommend that all presumptive TB cases undergo testing by a molecular based method, including cartridge based method

b. DST for at least rifampicin and isoniazid

c. DST for at least fluoroquinolones and second-line injectable agents

d. 0 out of 4 cases notified

e. Also recommended for sputum smear negative cases

f. Also recommended for sputum smear negative patients with abnormal chest X-ray

g. As of March 2014

h. New recommendation for 2014

i. Capacity to perform 2nd-line DST is available in-country but exact number of labs is not available

j. Only in 18/83 territories; proportion of microbiologically confirmed TB cases is > 50%

DIAGNOSTICS					
Kenya	**Myanmar**	**Russian Federation**	**South Africa**	**Uzbekistan**	**Zimbabwe**
5 in 2014	2 in 2012	117 in 2012	15 in 2012	7 in 2012	2 in 2012
5 in 2014	2 in 2012	110 in 2012	15 in 2012	3 in 2012	2 in 2012
2 in 2014	1 in 2014 [p]	Unknown [i]	Unknown [i]	3 in 2014	0 in 2014
2 in 2012	2 in 2012	Unknown	15 in 2012	3 in 2012	2 in 2012
70 in 2014 [g]	30 in 2014	107 in 2014	289 in 2014	19 in 2013	58 in 2014
No	No	Yes [a]	Yes	Yes	No
Yes	Yes [f]	Yes	Yes	Yes	Yes [e]
Retreatment, MDR-TB contacts, Cat 1 failures, and others	Retreatment cases (relapse and return after default); failures, close contacts of MDR-TB patients; all TB patients living with HIV/AIDS	All new TB patients	All individuals suspected of having TB	All new TB patients	Contacts of DR-TB, previously treated and failures
Unknown	34% in 2012	43.4% on average in 2012	Unknown	37.3% in 2013	44.5% in 2012 [p]
Unknown	Unknown	40.6% on average in 2012 [j]	Unknown	60% in 2013	Unknown
Unknown [l]	10.8% in 2012	Unknown	72% in 2012	10% in 2013	Unknown
100% in 2013	34% in 2012	94% on average in 2010	Unknown	90% in 2013	Close to 100% in 2012
100% in 2013	56% in 2012	See footnote [m]	42% in 2012	85% in 2013	70% in 2012
100% in 2012	0% in 2012 [c]	Unknown	Unknown	11% in 2013	100% in 2013 [n]
Unknown	$9.98 [p]	$60.00	Unknown	Unknown	$9.98

k. 1st-line culture and DST not routinely done in new cases. Approximation of retreatment cases tested for 1st line DST: 59%

l. 2nd-line not systematically done

m. In 2012, 13,612 laboratory confirmed MDRTB cases have been notified and 18,452 patients have been reported as started on MDR-TB treatment (26% of MDR-TB patients started on treatment without laboratory confirmation)

n. Two cases diagnosed with XDR-TB

o. In 2013, 236 cases have been notified with laboratory confirmed XDR-TB; 364 have been initiated on XDR-TB treatment. Thus, 35% of cases have been initiated on treatment with no laboratory confirmation

p. As observed by MSF

q. For this specific case, we are discussing sites rather than devices

r. This is from the Standards of TB Care in India, STCI, which are recommendations but are not in the guidelines

Continued overleaf ⋯

Key survey results discussed in this report are summarised here. Citations for the sources of all survey results, and the complete survey results, are available at: www.msfaccess.org/outofstep/

TREATMENT			
		Brazil	**India**
Do the national guidelines recommend Category 2 retreatment?		No	Yes
Is Intermittent treatment used?		Varies[a]	Yes
Is hospitalisation recommended for MDR-TB patients?		No	Yes[c]
NTP Program purchasing mechanisms	**DS-TB**	International procurement with agreement from PAHO	unknown
	DR-TB	Direct purchase, tender and GDF	unknown
What is the most decentralised level of treatment initiation?	**DS-TB**	Primary health units and referral secondary health units	Rural health post[b]
	DR-TB	Referral tertiary health units	Government medical college hospital or equivalent
Access to new molecules	**Compassionate use**	Yes	No formal CU but possible[g]
	Rapid registration process	No	Unknown[b]

a. Practised in one state
b. As observed by MSF
c. One week
d. In KaraKalpakstan region, hospitalisation is done according to certain criteria (critically ill patients); others are treated on Ambulatory care day 1 (ACD1). In other regions, patients are hospitalised, with out-patient treatment considered after six samples (smears/cultures) are negative
e. Any form of TB has to be hospitalised until smear conversion or for eight weeks; this also includes drug-sensitive TB

RESOURCE MOBILISATION		
	Brazil	**India**
Domestic funding[a]	a) 100% ($79.66 million) of domestic funding are spent on TB B) 84% of NTP budget ($87 million) domestically funded with 14% unfunded	57% of NTP budget ($67.34 million)
International funding[a]	2% international in 2013	37% of NTP budget ($103.74 million)
Plans to scale up national laboratory capacity for culture and DST?	Yes	Unknown
How many additional culture and DST laboratories planned?	Unknown[c]	Unknown
Plans to scale up Xpert MTB/RIF?	Yes	Yes
How many additional Xpert MTB/RIF devices planned?	50[e]	1029 by 2016

a. In 2013
b. As observed by MSF
c. Brazilian MoH is evaluating the extension of culture network according to the context of the operation of the Xpert Network
d. As of 27 September 2013
e. Four-module devices
f. For a total of 440 devices
g. Expansion of Xpert MTB/RIF implementation in correctional services, mines and perimining communities
h. To have a total of five laboratories performing culture and DST by 2016

TREATMENT					
Kenya	**Myanmar**	**Russian Federation**	**South Africa**	**Uzbekistan**	**Zimbabwe**
Yes	Yes	No	No	Yes	Yes
No	No	No	No	Yes[b]	No
No	No	Yes[e]	Yes[f]	Varies[d]	No
Open international tender; GDF; Kenya Association for Prevention of TB and Lung Disease (KAPTLD)	Direct purchase, GDF and Maclocd Co[b]	National tendering process	Tendering process	GDF[b]	UNDP purchases drugs through UNICEF
100% from GDF, GF and MSF	GDF[b]	National tendering process[b]	Tendering process	GDF[b]	International tendering process; 90% through GDF
Approved health centres (level 3)[b]	Health centre, urban or private clinic	Rural health clinic or health post	Urban/rural health clinic[b]	District hospital	Rural clinic[b]
Approved health centres (level 3)[b]	Regional/state TB treatment centres	Rural health clinic or health post	Health centre	Regional hospital	District hospital
No formal CU but possible[b]	No[b]	No formal CU but possible[b,i]	No formal CU, clinical access program[b]	No[b]	Yes[b]
No[b]	No[h]	No[b]	Yes	No[b]	Yes

f. Patients diagnosed with MDR-TB who are smear microscopy positive will be hospitalised at the decentralised DR-TB units for up to eight weeks or until they become smear negative on two consecutive tests.

g. Not in the Indian Drugs and Cosmetics act, Currently using the provision of importation for personal use for Bdq

h. Previous exception made for TB drug in 2011

i. There is legislation for importation of non-registered drugs in Russia for "life-saving" situations (not called CU)

RESOURCE MOBILISATION					
Kenya	**Myanmar**	**Russian Federation**	**South Africa**	**Uzbekistan**	**Zimbabwe**
24% of NTP budget ($13.2 million)	2% of NTP budget ($0.72 million)	100% of NTP budget ($1,592 million)	97% of NTP budget ($460.75 million)	75% of NTP budget ($76 million)	4% of NTP budget ($1.52 million)
15% of NTP budget ($8.25 million)	39% of NTP budget ($14.04 million)	Unknown	3% of NTP budget ($14.25 million)	25% of NTP budget ($76 million)	39% of NTP budget ($14.82 million)
Yes	Yes	Yes[b]	Unknown	No	Yes
Unknown	3[h]	Unknown	Unknown	Unknown	4
Yes	Yes	Yes	Yes	Yes	Unknown
Additional 370 by 2016[f]	14 in 2014	Unknown	Unknown[g]	6[d]	Not applicable[g]

GLOSSARY

Active case finding: Strategy of actively screening and diagnosing individuals belonging to groups at high risk of TB (ie. HIV co-infection, miners, etc.). Risk groups vary depending on epidemiological profiles of TB in a given country.

Category II (Category 2) treatment: One drug, streptomycin, is added to the standard first-line drug regimen and the regimen extended to eight months. WHO recommended this treatment option when DST is not routinely available and in areas of low risk of MDR-TB.

Clinical trials: Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions (eg drugs, diagnostics, devices, therapy protocols) to evaluate the effects on health outcomes.

Compassionate use: The terms "compassionate use," "expanded access" or "special access" programmes have essentially the same meaning. They refer to programmes that are intended to provide potentially lifesaving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial. It 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 national legislation that establishes under which conditions the drug is made available. Refer to Annex 5 (*Use of experimental drugs outside of clinical trials "compassionate use"*) of the WHO Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008.

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

Consilium: An advisory body, as in the Russian Federation's TB doctors' consilium.

Continuation phase: The treatment period after the intensive phase; usually has a reduction in the number of drugs that need to be taken. Length can be variable depending on the type of TB treated. For DS-TB, the continuation phase is two drugs for four months. For more info, please consult: http://www.cdc.gov/tb/topic/treatment/tbdisease.htm

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

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

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

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

Essential Medicines List (EML): Lists the essential medicines that should be available that satisfy the priority health care needs of the population. The medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford.

Ex-works: A commercial term (incoterm 2010) meaning that the seller delivers when the goods are placed at the disposal of the buyer at the seller's premises or another named place (i.e. works, factory, warehouse etc.), not cleared for export and not loaded on any collecting vehicle.

Extensively drug-resistant TB: see XDR-TB

External quality assessment (EQA): a system for objectively checking the laboratory's performance using an external agency or facility. EQA allows for comparison of a laboratory's testing to a source outside the laboratory. This comparison can be made to the performance of a peer group of laboratories or to the performance of a reference laboratory. Please consult http://www.who.int/ihr/training/laboratory_quality/10_b_eqa_contents.pdf

Extra-pulmonary TB: Form of TB where *M. tuberculosis* infects parts of the body other than the lungs. This is most commonly the lymph nodes, bones, central nervous system, cardiovascular and gastrointestinal systems.

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

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

Group 5 TB medicines: Anti-tuberculosis drugs with unclear efficacy or an unclear role in MDR-TB treatment. These drugs are critically important as third-line or salvage therapy for XDR-TB, but are not recommended by WHO for routine use in MDR-TB patients. Key Group 5 medicines are clofazimine, linezolid, and imipenem/cilastatin.

Low-income country (LIC): World Bank income classification for economies with gross national income per capita of US$1,045 or less for World Bank fiscal year 2015. Please consult http://data.worldbank.org/about/country-and-lending-groups

Lower-middle-income country (LMIC): World Bank income classification for economies with gross national income per capita more than $1,045 but less than $4,125 for World Bank fiscal year 2015. Please consult http://data.worldbank.org/about/country-and-lending-groups

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

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

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

M. Tuberculosis: Mycobacterium Tuberculosis: A pathogenic bacterial species of the genus Mycobacterium and the causative agent of most cases of TB. First discovered in 1882 by Robert Koch.

Point-of-Care testing (POC): Testing at the point-of-care means that diagnosis is carried out as close as possible to the site of patient care. The driving notion behind point-of-care testing is having a test as convenient to the patient as possible and giving immediate results that can lead to prompt initiation of treatment.

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

Second-line drugs: Second-line drugs are used when the first-line drugs are no longer effective to cure a patient. In the case of tuberculosis, they are less effective and have many more side-effects than first-line drugs.

Standard treatment guidelines (STG): STGs are also known as standard treatment schedules, standard treatment protocols or therapeutic guidelines. Each pharmaceutical treatment should include for each health problem the name, dosage form, strength, average dose (paediatric and adult), number of doses per day, and number of days of treatment. For additional information please consult: http://www.who.int/medicines/technical_briefing/tbs/10-PG_Standard-Treatment-Guidelines_final-08.pdf

Stringent regulatory authority (SRA): Is a regulatory authority which is (a) a member of the International Conference of Harmonization (ICH); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and World Health Organization (WHO); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein. Please consult http://www.ich.org

TB Alliance: The TB Alliance is a not-for-profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB patients currently on such therapies, and improve treatment of latent infection. The TB Alliance is committed to ensuring that approved new drug regimens are affordable, widely adopted and available to those who need them.

TRIPS flexibilities: TRIPS (Trade-Related aspects of Intellectual Property) Agreement provides countries with a minimum standard of intellectual property protection on pharmaceuticals and other products; flexibilities relate to legal measures that give countries the right to overcome IP barriers where they hinder access to medicines, or undermine public health.

Upper-middle-income country (UMIC): World Bank income classification for economies with gross national income per capita between $4,125 to less than $12,748 for World Bank fiscal year 2015. Please consult http://data.worldbank.org/about/country-and-lending-groups

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

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

ABBREVIATIONS

CU – Compassionate use

DR-TB – Drug-resistant tuberculosis

DST – Drug susceptibility testing

DS-TB – Drug-sensitive tuberculosis

EMA – European Medicines Agency

EML – Essential medicines list

EP-TB – Extra-pulmonary TB

EQA – External quality assessment

FDC – Fixed-dose combination

FSU – Former Soviet Union

Global Fund/GFATM – Global Fund to Fight AIDS, Tuberculosis, and Malaria

HIV – Human immunodeficiency virus

LIC – Low-income country

LMIC – Lower-middle income country

LPA – Line probe assay

MCC – Medicines Control Council (South Africa)

MDR-TB – Multidrug-resistant tuberculosis

MGIT – Mycobacteria Growth Indicator Tubes

MIC – Middle-income country

MOH – Ministry of Health

MSF – Médecins Sans Frontières

NGO – Non-governmental organisation

NMRA – National medicines regulatory authority

NTP – National TB programme

NTRL – National TB reference laboratory

OR – Operational research

PMDA – Pharmaceutical and Medical Devices Agency (Japan)

PQ – Prequalification

R&D – Research and development

STG – Standard treatment guidelines

TB – Tuberculosis

UMIC – Upper-middle income country

USAID – US Agency for International Development

US FDA – United States Food and Drug Administration

WHA – World Health Assembly

WHO – World Health Organization

XDR-TB – Extensively drug-resistant tuberculosis

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