



# Four Years and Counting

**Slow scale-up of newer MDR-TB drugs covers less than 5% in need**

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## **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 health care. Founded in 1971, MSF has operations in over 60 countries today.

MSF has been involved in TB care for 30 years, often working alongside national health authorities to treat patients in a wide variety of settings, including chronic conflict zones, urban slums, prisons, refugee camps and rural areas. MSF's first programmes to treat multidrug-resistant TB opened in 1999. MSF has TB treatment projects in 24 countries; it is one of the largest non-governmental providers of treatment for drug-resistant TB. In 2016, MSF supported more than 20,000 TB patients on treatment, including 2,700 patients with drug-resistant forms of TB.

Largely in response to the inequalities surrounding access to HIV/AIDS treatment between rich and poor countries, MSF launched the Access Campaign in 1999. Its sole purpose has been to push for access to, and the development of, life-saving and life-prolonging medicines, diagnostics and vaccines for patients in MSF programmes and beyond.

## **About endTB**

In 2015, MSF, Partners in Health and Interactive Research & Development launched the endTB project. Expand new drug markets for TB (endTB) seeks to improve treatment outcomes for people with multidrug-resistant TB (MDR-TB). See page 10 for more information.

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Slow scale-up of newer MDR-TB drugs covers only 5% in need

### **To access the report online:**

[msfaccess.org/MDR-TB-issue-brief-2017](http://msfaccess.org/MDR-TB-issue-brief-2017)

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## Introduction

An estimated 580,000 people fell ill with multidrug-resistant (MDR) forms of tuberculosis (TB) in 2015, including 100,000 with rifampicin-resistant TB (RR-TB). Only 132,000 cases of MDR-TB were diagnosed, and only 125,000 people began MDR-TB treatment. An estimated 250,000 people died from MDR/RR-TB in 2015.<sup>1</sup>

This issue brief examines current opportunities to optimise MDR-TB treatment and to address the persistent access challenges that put treatment out of reach for people struggling to survive this deadly disease.

Several factors contribute to high levels of drug resistance and the low proportion of people who need MDR-TB treatment that are successfully diagnosed and treated. Delayed diagnosis and misdiagnosis lead to ineffective treatment. Even if people with MDR-TB are successfully diagnosed, treatment remains complex, onerous, expensive and, in some countries, unavailable to treat all patients in need. Treatment for MDR-TB can last for two years and include eight months of painful daily injections and nearly 15,000 pills. The current price for a 24-month course of conventional treatment ranges from US\$2,000 to US\$20,000.

Cure rates for such arduous regimens are abysmal: just 52% for patients with MDR-TB and just 28% for patients with XDR-TB. Whether they beat the odds or do not, people treated with these regimens pay a terrible price. Side effects such as permanent deafness are common, and many people face catastrophic healthcare costs, unemployment and separation from families and communities. This bleak reality persists despite changes to WHO guidelines, which recommend the use of innovative rapid molecular testing, a shorter treatment regimen for MDR-TB, and the newer drugs bedaquiline and delamanid.

Without changes to current TB prevention and treatment, the incidence of MDR-TB and extensively drug-resistant TB (XDR-TB) will continue to increase in high-burden countries, according to epidemiological modelling.<sup>2</sup> We have the strategies we need to guide these changes. Although we desperately need more research and development efforts to deliver shorter and better treatments and more adapted diagnostics for MDR-TB, we already have improved tools at our disposal today that we are failing to use to reduce suffering and death from TB.

## Less than 5% of people have access to newer medicines to treat MDR-TB

Conventional MDR-TB treatments last almost 24 months and are associated with severe side effects and poor outcomes. Two newer drugs – bedaquiline and delamanid – can help increase cure rates and reduce mortality, but scale-up is lagging for several reasons.<sup>3</sup> Médecins Sans Frontières (MSF) estimates that less than 5% of people with MDR-TB who could have benefitted from these lifesaving newer medicines were treated with them in 2016.<sup>4</sup> Data on global use of the newer drugs indicate that only 10,164 people so far had received bedaquiline and 688 people had received delamanid as of July 2017.<sup>5</sup>

## Treatment outcomes in MSF projects using bedaquiline and delamanid

MSF supports national TB programs to introduce bedaquiline and delamanid according to WHO recommendations, including off-label use of the drugs in paediatric patients or for durations beyond 24 weeks, with very promising results. As of July 2017, a total of 1,554 patients had been treated with the newer drugs in 13 MSF projects across 11 countries. Of those treated, 1,110 patients received bedaquiline, 444 received delamanid and 117 received a combination of both medicines. Approximately 70 of these patients were under 18 years of age; roughly 300 patients received treatment for longer than 24 weeks.

## **Promising new results: 48<sup>th</sup> Union World Conference on Lung Health**

In yet to be published data which will be presented at the October 2017 Union World Conference on Lung Health, MSF and partners have documented promising results on the safety and efficacy of treatment regimens containing bedaquiline and/or delamanid, including vastly improved outcomes compared to standard MDR-TB treatment. Results from these studies will be presented on 13 October during the following oral abstract sessions:

### **The Union/CDC late-breaker session on TB**

10:30 to 12:00 – Plenary Hall

- Early safety and efficacy of bedaquiline and delamanid combination for drug-resistant TB in Armenia, India and South Africa (OA-2905-13)

### **MDR-TB treatment: pharmacovigilance and adverse event outcomes from the field**

10:30 to 12:00 – Hall 13 (Jalisco Hall)

- Safety of multidrug-resistant tuberculosis treatment amongst patients receiving bedaquiline in a compassionate use programme in Armenia and Georgia (OA-163-13)

### **MDR-TB: treatment outcomes using new drugs**

16:00 to 17:30 – Hall 13 (Jalisco Hall)

- Culture conversion and reversion of multidrug-resistant tuberculosis patients receiving bedaquiline in a compassionate use programme in Armenia and Georgia (OA-188-13)
- Bedaquiline and linezolid-based regimens for fluoroquinolone-resistant MDR-TB: how much better is it? (OA190-13)
- Outcomes of multidrug-resistant tuberculosis patients receiving bedaquiline in a compassionate use programme in Armenia and Georgia (OA-192-13)
- Delamanid for rifampicin-resistant tuberculosis: an observational cohort study from Khayelitsha, South Africa (OA-193-13)

## **Off-label use of bedaquiline in children and adolescents**

Data from 27 children and adolescents under 18 years of age who started bedaquiline-containing regimens between November 2014 and January 2017 were collected from MSF-supported TB treatment programmes in South Africa, Tajikistan and Uzbekistan, and from the National TB Programme in Belarus. No patients were HIV positive. Diagnoses for 17 (63%) patients were confirmed by mycobacterial culture. Baseline sputum smears from 19 (70%) patients were positive for acid-fast bacilli. Most patients (18/27, 67%) had XDR-TB; 6 (22%) had MDR-TB with fluoroquinolone resistance; and 3 (11%) had MDR-TB with resistance to a second-line injectable drug. For the 10 patients without positive mycobacterial cultures, drug susceptibility was presumed from contact history. Thus, for all patients, the decision to use bedaquiline was based on confirmed or presumed extensive drug resistance that resulted in the inability to construct an effective treatment regimen.

The mean duration of bedaquiline treatment for the 20 children and adolescents who completed therapy was 172 days. As of February 24, 2017, all 23 patients who remained on treatment and had data available were culture negative; 14 of these 23 patients were culture positive at baseline. No clinical signs suggesting treatment failure were noted for patients in the cohort. These preliminary results suggest that bedaquiline can be used safely in children over 12 years of age with appropriate monitoring, and could be considered in younger children in selected circumstances when no other options are available and benefits are likely to outweigh risks. The data also support the expansion of access to bedaquiline for children in order to reduce the need for second-line injectable drugs, which are strongly associated with irreversible toxicity.<sup>6</sup>

## Use of delamanid

While delamanid has had limited use outside clinical trials, MSF results from a multi-centric retrospective analysis of patients receiving delamanid under programmatic conditions show good tolerability and treatment response at 6 months, with 68% culture conversion at 6 months.<sup>7</sup> This retrospective study comprises all patients started on MDR-TB regimens containing delamanid in MSF-supported sites before 1 March 2016.

From February 2015 to February 2016, a total of 53 patients from 7 countries (Armenia, Belarus, Georgia, India, Russia, Swaziland and South Africa) started a delamanid-containing regimen. Of these, 46 (86.8%) received delamanid through a compassionate use programme. Most patients had been treated previously with second-line drugs (48/53, 90.6%), experienced MDR-TB treatment failure (32/53, 60.4%), exhibited resistance to second-line TB drugs (41/51, 80.4%), or had extensive pulmonary disease (40/45, 88.9%). Almost all patients (52/53, 98.1%) received a delamanid-containing regimen because a regimen including a minimum of four other second-line drugs likely to be effective could not be composed according to WHO recommendations.

Of the patients who were culture positive at start of delamanid treatment, 67.6% (25/37) culture converted by 6 months. At 6 months, 73.6% (39/53) of patients had a favourable response, 13.2% (7/53) had died, 7.5% (4/53) remained culture positive, 3.8% (2/53) were lost to follow-up, and 1.9% (1/53) were declared to have a failure in treatment as a result of a serious adverse event.

## Major barriers to access persist

Marketing authorisation was first granted for bedaquiline in 2012 (US Food and Drug Administration) and for delamanid in 2014 (European Medicines Agency). The WHO issued interim guidance on the use of bedaquiline and delamanid in MDR-TB treatment regimens in 2013 and 2014, respectively.

Although these promising newer drugs have now been on the market for several years, they remain almost totally out of reach for people who can benefit. The two drugs offer new hope for people struggling to survive this deadly disease, but critical barriers to uptake have yet to be addressed. In the 29 countries assessed in the 2017 edition of the Out of Step report\*, failures at the country level to proactively introduce newer medicines – and at the manufacturer level to register them and ensure their affordability – have put scale-up at a virtual standstill.

## Slow registration by pharmaceutical companies

Most pharmaceutical companies are not meeting their responsibility to urgently accelerate registration of newer treatments and key companion medicines in TB-affected countries.

Otsuka, the producer of delamanid, has not sought to register the product widely. Among all 30 high MDR-TB burden countries defined by WHO for the period 2016-2020, India is the single country in which delamanid is registered. The European Union, Japan, Hong Kong, South Korea and Turkey are the only other places where delamanid is registered. Regulatory assessments are ongoing in China, Indonesia, South Africa and the Philippines.

Johnson & Johnson/Janssen (J&J/Janssen), the producer of bedaquiline, has so far registered the drug in 18 countries; dossiers are pending in 16 others and have been rejected in four (Azerbaijan, Georgia, Kazakhstan and Kyrgyzstan) due to the lack of phase III data.

Among the 30 high MDR-TB countries, there are 11 countries in which bedaquiline has either not been registered or a dossier has not been submitted for review: Angola, Democratic People's Republic of Korea, Democratic Republic of Congo, Mozambique, Myanmar, Pakistan, Papua New Guinea, Somalia, Tajikistan, Ukraine and Zimbabwe.

\* Published by MSF and the Stop TB Partnership, the Out of Step 2017 report surveys prevention, testing and treatment policies and practices in 29 countries that represent 82% of the global TB burden. Available at: [www.msfacecess.org/outofstep2017](http://www.msfacecess.org/outofstep2017).

Although lack of registration is a key barrier to scaling up access to the newer drugs, a majority of countries have viable options – and therefore a responsibility – to treat patients with the newer drugs now. Of the 29 countries surveyed in Out of Step 2017, 25 allow access to unregistered TB medicines through compassionate use programmes, import waivers, or by other means. Twelve countries also are enrolled in the WHO Collaborative Registration Procedure, described on page 8, which accelerates approval of originator and generic medicines, including for TB.

These important mechanisms can play a pivotal role in addressing tragically slow uptake of newer TB drugs; however, they are largely underutilised by national health authorities today.

## **Slow introduction of newer TB treatment by national health authorities**

Findings from Out of Step 2017 show that 79% (23) of countries surveyed include bedaquiline in their national treatment guidelines; 62% (18) include delamanid in their guidelines.<sup>8</sup> MSF has TB projects in 18 of the countries surveyed. These levels of adoption could be different in other contexts where MSF is not working.

In certain conditions, treatment for MDR-TB can be shortened to nine months. For people who are eligible, shortened treatment is equally effective, spares months of terrible side effects, and saves money. Only 13 countries (45%) surveyed recommend these new, shorter treatments in their guidelines; none have made them widely available.

## **High drug prices a burden for national TB programmes**

### ***Delamanid***

The lowest price for a six-month treatment course of delamanid of US\$1,700 – or US\$283 per month – is available through the Global Drug Facility (GDF) for countries that qualify for TB funding from the Global Fund to Fight HIV, TB and Malaria (Global Fund). A study published in the Journal of Antimicrobial Chemotherapy estimates that delamanid can be produced for US\$4.89 to US\$15.57 per month – a potential 96% decrease from the current lowest price through the GDF.<sup>9</sup> Assuming the current lowest average cost of US\$2,000 for a conventional MDR-TB regimen, adding delamanid alone at its current cost doubles the overall cost of treatment. This financial burden remains a serious challenge for national TB programmes working to scale up access to newer drugs.

### ***Bedaquiline***

Bedaquiline was initially available through the GDF via a tiered pricing structure, with a six-month course costing US\$900 for low-income countries and US\$3,000 for middle-income countries. Although WHO recommends against donation programmes for medical products<sup>10</sup>, USAID and J&J/Janssen announced a bedaquiline donation programme in April 2015, whereby most countries that qualified for TB grants from the Global Fund could obtain bedaquiline as a donation through the GDF.<sup>11</sup> After more than two years, however, around only one-third of the 30,000 treatment courses allocated for the programme had been dispensed as of August 2017. This suggests a lack of political will at country level to provide broader access to newer medicines.

It is noteworthy that the two countries with the highest use of bedaquiline, South Africa and the Russian Federation, do not have access to this donation: the South African Ministry of Health does not use GDF as a supply channel; the Russian Federation does not qualify for Global Fund grants. Adding bedaquiline to already expensive MDR-TB treatment regimens significantly increases their cost. The price for a six-month course of bedaquiline is currently US\$745 in South Africa and US\$1,970 in the Russian Federation.

## **Fair licensing can increase availability of newer drugs**

Licensing agreements have the potential, in the short term, to increase the number of countries where newer drugs are registered. In the longer term, affordability of newer drugs may improve once technology transfer arrangements are completed and multiple sources of manufacturing exist to compete in the same markets.

## **Bedaquiline**

In January 2013, J&J/Janssen entered into a licensing agreement with the Russian company, Pharmstandard, to register and commercialise bedaquiline in the countries of the Commonwealth of Independent States (CIS) and Georgia. Registration has been granted in five countries (Armenia, Moldova, the Russian Federation, Turkmenistan and Uzbekistan) and is pending in Belarus. Due to lack of phase III data, submissions have been rejected in Azerbaijan, Georgia, Kazakhstan and Kyrgyzstan. Pharmstandard has yet to submit a dossier in Tajikistan, the last CIS country where no regulatory activity has been initiated for bedaquiline.

Russian pharmaceutical companies currently face challenges registering medicines in Ukraine. An agreement between J&J/Janssen and Pharmstandard is under discussion regarding a transfer of ownership that would allow the local branch of Janssen to submit a regulatory filing and serve as the marketing authorisation holder in the Ukraine. This will secure long-term supply of bedaquiline.

Pharmstandard began supplying bedaquiline tablets produced at their Ufa site on the Russian market in May 2017. Until then, they had supplied bedaquiline tablets manufactured by J&J/Janssen in India, which were repacked by Pharmstandard.

According to the initial tiered pricing structure established by J&J/Janssen in December 2014, a six-month treatment course with bedaquiline should have cost US\$30,000 in the Russian Federation, which has been classified as a high-income country since 2013. Currently, Pharmstandard supplies bedaquiline on the Russian market at a cost of US\$1,970 per treatment. However, no further competition is expected since Pharmstandard has exclusivity rights in the country. The broader impact of the agreement between J&J/Janssen and Pharmstandard on worldwide bedaquiline pricing will not be clear until the end of the USAID and J&J/Janssen donation programme.

## **Delamanid**

In July 2017, Otsuka announced a non-transferable license with the Russian company, R-Pharm, for registration and supply of delamanid in the countries of the Commonwealth of Independent States (CIS) and Georgia. Manufacturing steps to be transferred between the two companies are still under discussion. Otsuka will supply delamanid tablets manufactured in Japan until technology transfer is completed. RPharm's regulatory submission in the Russian Federation is pending. If a local trial waiver is granted, marketing authorisation could be granted in 12 months. Meanwhile, registration in other countries covered by R-Pharm's license is expected to begin.

In August 2017, Otsuka announced an agreement with Mylan for supply and registration of delamanid in South Africa and India, as well as all countries where Otsuka has no commercial presence. Mylan was already granted marketing authorisation in India and submitted a registration file in South Africa in July 2017. The companies have yet to confirm which other high MDR-TB burden countries will be included in the agreement. Furthermore, feasibility studies are just starting for the manufacture of delamanid tablets by Mylan, with technology transfer to follow.

Otsuka maintains that delamanid's current price of US\$1,700 per treatment, established in February 2016, is justified by the current manufacturing cost structure at its Japanese plant coupled with low worldwide demand. Technology transfers at Mylan and R-Pharm could facilitate lower manufacturing costs. Consequently, this could lead to a more affordable commercial price for the drug – even if the licensing agreements reportedly do not contain commitments to that effect and avoid competition between the three companies on the same markets, which would be a more powerful driver of affordability.

We urge Otsuka, R-Pharm and Mylan to register delamanid in as many high MDR-TB burden countries as possible, and to prioritise registration in countries where either the WHO Collaborative Registration Procedure or local expedited registration procedures exist. We also urge all three companies to proceed with effective technology transfers in order to allow countries to treat as many people as possible with existing TB funding.

## ***In Focus: India***

In June 2017, Otsuka-Mylan obtained a local trial waiver from the Drugs Controller General of India, which led to fast-track registration for delamanid. Otsuka and the Indian government have announced plans to make an initial 400 courses of delamanid available for patients treated in Revised National TB Control Programme (RNTCP) facilities through the Delamanid Clinical Access Programme (DCAP). Indian health authorities will use this access program to control the introduction of delamanid following local registration, similarly to the way bedaquiline was introduced in the country.

Now that marketing authorisation has been granted, the DCAP should start as soon as possible in at least as many RNTCP sites as where bedaquiline is dispensed. However, the clinical protocol is still under discussion and authorised sites have yet to be identified. Considering the number of people in need of newer MDR-TB medicines in India, 400 courses will fall far short of meeting needs throughout the country.

Compassionate use access for delamanid in India is maintained by Otsuka-Mylan in parallel with the DCAP, and is crucial to allow private physicians and entities outside RNTCP network to dispense delamanid on an individual patient basis.

## ***In Focus: South Africa***

In July 2017, after many months of delay, Mylan submitted a registration dossier for delamanid to the South African Medicines Control Council (MCC), who we urge to prioritise the assessment considering the public health needs in the country.

On World TB Day 2017, Otsuka, in partnership with South Africa's National Department of Health, announced that 400 courses of delamanid would be provided for select patients through the Delamanid Clinical Access Programme (DCAP). In South Africa, the DCAP is intended to provide access to delamanid before the product is granted local marketing authorisation. However, the limited number of treatments and restrictive inclusion criteria will not ensure access to delamanid for all patients who need it. Furthermore, implementation of the programme has been consistently delayed. Only 20 patients were enrolled on treatment through the programme as of August 2017.

Compassionate use access for delamanid in South Africa is maintained by Otsuka in parallel with the DCAP and is crucial for patients who do not meet the narrow inclusion criteria of the DCAP.

## **Spotlight on MDR-TB diagnostics**

Conventional culture and drug-susceptibility testing (DST) are the gold standard for the diagnosis of MDR-TB; however, these methods require specialised laboratory facilities and skilled staff, which restricts their use to central laboratories. This is the case for the newly WHO-endorsed rapid molecular diagnostics, such as first-line and second-line line-probe assays (LPAs).<sup>12, 13</sup> It is not uncommon for MDR-TB diagnosis to take several weeks, if not months, because centralised testing requires efficient transport networks for delivery of both specimens and results. The consequences for patients who go undiagnosed or are diagnosed too late as a result of such delays can be devastating.<sup>14</sup>

Simpler rapid molecular diagnostics have entered the market in recent years.<sup>15</sup> One such test, Xpert MTB/RIF, is recommended by WHO as the initial test for TB. It detects both TB and rifampicin resistance in only two hours and can be used by non-skilled staff. The near point-of-care (POC) platform can be used in decentralised settings; however, because it requires constant power supply and air-conditioning in tropical climates, it is usually placed in facilities at the district and sub-district levels.

Although Xpert MTB/RIF was endorsed by WHO in 2010 and has been adopted widely in resource-limited settings,<sup>16</sup> a substantial diagnosis gap persists. Only 16% of TB cases notified to the WHO in 2015 received DST for rifampicin; of these, only 36% underwent second-line DST.<sup>17</sup> The End TB Strategy calls for early diagnosis of TB including universal DST; however, only 33% of the thirty high MDR-TB burden countries have a national policy specifying Xpert MTB/RIF as the initial diagnostic test for all people presumed to have TB.<sup>6</sup> Barriers to roll-out include high overall testing costs, and lack of training, quality assurance and maintenance support.<sup>18, 19</sup> High rates of empirical treatment,<sup>20, 21</sup> treatment gaps,<sup>22</sup> and ongoing high mortality rates<sup>23, 24</sup> have limited the clinical impact of Xpert MTB/RIF.

New POC molecular technologies that can facilitate further decentralisation of testing could help bridge the gap in case detection. Although there are several such technologies in the pipeline, all are in early stages of development.<sup>25</sup> WHO recently endorsed Xpert MTB/RIF Ultra, which is more sensitive than Xpert MTB/RIF for diagnosing smear-negative, culture-positive TB, paediatric and extrapulmonary TB, and HIV-associated TB.<sup>26</sup> It may also have superior performance for rifampicin resistance detection, but further studies are needed to confirm this feature.<sup>27</sup> Cepheid has developed a new true POC system, GeneXpert Omni, which is a small, portable, battery-operated instrument suitable for use in remote settings. It is expected to be launched by mid-2018.<sup>28</sup> The development of a new GeneXpert cartridge to test resistance to isoniazid, fluoroquinolones and injectable agents,<sup>29, 30</sup> in combination with Omni, would represent a step forward in ensuring access to universal DST, particularly in the context of improved MDR-TB regimens. According to Cepheid, the new XDR cartridge is expected to be released in late 2018 or early 2019.<sup>31</sup>

## **New Global Fund policies threaten MDR-TB treatment scale-up**

Many national TB programmes use the Global Drug Facility (GDF) – a pooled procurement mechanism – to procure quality-assured TB medicines, particularly MDR-TB medicines financed through grants from the Global Fund. However, the Global Fund has changed its co-financing and allocation policies to fully or partially restrict middle-income countries' eligibility for funding support, particularly for countries with lower burden of disease. Several countries with high burdens of DS-TB and MDR-TB are affected by the new policies. For example, countries in Eastern Europe and Central Asia (EECA) that are now funded by the Global Fund are expected to substantially increase national co-financing of second-line TB drugs and/or prepare for transition as their eligibility for funding winds down.

Pooled procurement facilitated by the GDF for MDR-TB medicines has ensured availability of quality medicines at the lowest available prices for the last ten years, but the Global Fund resource constraints already threaten efforts to expand access to lifesaving TB treatment. As countries are no longer eligible for Global Fund support, they will no longer have access to this pooled procurement mechanism. The co-financing of MDR-TB drugs will result in parallel procurement streams. This could hamper access to affordable, quality-assured MDR-TB medicines because quantities required by individual countries often do not meet manufacturers' minimum order requirements.

Global Fund policies have been overly reliant on income classification for determining funding allocations and transition plans in the EECA region compared to other criteria. We strongly recommend that the Global Fund supports independent risk assessments of the potential impact of funding and policy changes on procurement and treatment scale-up for grantees in the EECA region and beyond. Changes in policy should not be enacted until the results are available, and the findings should be used to strengthen plans for progressive national co-financing of key interventions, including procurement of TB commodities. The Global Fund should also offer or facilitate technical and legal assistance for countries affected by policy changes to ensure as smooth a transition as possible. Follow-through in each of these areas is essential to safeguarding the expansion of access to affordable, quality TB treatment in the region.

## ***Strategies to increase affordability***

When higher volumes of medicines are purchased, suppliers are willing to offer more affordable prices. This simple purchasing rule prompted the development of pooled procurement mechanisms, whereby multiple customers combine their orders at a single entry point and benefit mutually from more affordable prices. This is how the Global Drug Facility (GDF), an initiative from the Stop TB Partnership, has worked on TB medicines since 2001.

GDF consistently offers the most sustainable prices for quality-assured MDR-TB medicines (see Appendix) by pooling demand for TB medicines across nearly 140 countries while implementing a stringent quality assurance policy together with a competitive and transparent tendering process. Being the unique international pooled procurement mechanism currently working at this scale, GDF prices should serve as a benchmark for national TB programmes and other stakeholders working to improve access to MDR-TB medicines. As shown in the Appendix, prices increased between 2016 and 2017 for only two medicines, prothionamide and cycloserine, due to increased prices of the active ingredients.

In order to secure more affordable prices, GDF strives to improve the accuracy of pooled demand forecasts which, in turn, provide manufacturers with improved visibility for production planning. We urge countries and the Global Fund to contribute to efforts to provide more accurate MDR-TB medicines forecasts, which are essential to secure supply of quality-assured MDR-TB medicines and to attract manufacturers to this relatively niche market. GDF also works with manufacturers to push for longer shelf lives for TB medicines to reduce the likelihood of medicine expiring at health facilities, which leads to savings for national TB programmes.

It is compulsory for countries with an MDR-TB grant from the Global Fund to purchase MDR-TB medicines from GDF. Countries purchasing medicines outside of this specific can also strive to improve people's access to affordable, quality-assured TB medicines by adapting their national procurement rules to continue procuring through GDF. Countries with local manufacturers of TB medicines should create incentives for these companies to meet international quality assurance standards and bid in GDF international tenders in order to contribute to ensuring quality-assured, affordable MDR-TB medicines are available worldwide.

Funding cuts by international donors may prompt many countries to procure MDR-TB medicines through national government tenders, which is likely to lead to higher prices and possibly the procurement of medicines that are not quality-assured. For most countries, the volumes of MDR-TB treatment required to meet national needs may provide insufficient incentive for manufacturers of quality-assured products to systematically bid in their national tenders. Unlike other markets such as HIV medicines, healthy competition across suppliers in the niche MDR-TB drug market requires pooled procurement mechanisms.

## **WHO Collaborative Registration Procedure: an untapped resource**

In 2015, WHO launched the WHO Collaborative Registration Procedure (CRP) to facilitate access to generic or originator medicines, including TB medicines, for public health needs in developing countries. Participating national drug regulatory authorities (NDRAs) have 90 days to review the dossiers of stringent drug regulatory authority (SDRA)-approved or WHO prequalified products, under confidentiality, in a globally harmonised format aligned with the same system used for WHO prequalification. Through this process, NDRAs can follow their national legislation and responsibilities, collect fees, and develop risk-management and pharmacovigilance plans with applicants. Using this procedure ensures that medicines can get to the people who need them faster.

According to the WHO website, Macleods is currently the only generic manufacturer of WHO-prequalified TB medicines that has used the procedure in an extensive manner to register their products – and have done so in around ten countries. More generic and originator manufacturers should consider the advantages of the procedure as an efficient tool for accelerating registration of their products.

Considering the likely impact of the new Global Fund policies described above, countries should not rely on import waivers alone in order to import TB medicines. Countries, and high-burden ones in particular, should work actively to join the CRP to register new medicines. In parallel, manufacturers should proactively use this mechanism, or invest in the registration process in countries not yet part of the CRP mechanism. Joint efforts will ensure quality-assured medicines can be procured in a sustainable manner through national tenders.

WHO has also initiated a pilot project to expand the CRP to medicines with marketing authorisations granted by stringent regulatory authorities. J&J/Janssen is part of this pilot, with bedaquiline dossier assessments ongoing in eight sub-Saharan African countries (Burundi, Cameroon, Ghana, Kenya, Nigeria, Rwanda, Tanzania and Uganda).

## **Spotlight on paediatric TB formulations and critical companion medicines for MDR-TB**

### **New paediatric medicines available, but unmet needs remain**

Children have long been neglected in TB care due to the difficulty of diagnosing and treating the disease. WHO-recommended paediatric fixed-dose combination treatments for DS-TB have been available since December 2015, but governments have been slow to ensure the formulations reach children who need them.

For MDR-TB, it is likely that new quality-assured, child-friendly formulations for cycloserine, levofloxacin and moxifloxacin should shortly become WHO prequalified as they were recently granted Expert Review Panel approval.<sup>32</sup> They come in addition to pre-existing clofazimine 50mg soft capsules and linezolid oral suspension, as well as ethionamide 125mg dispersible tablet which was recently prequalified by the WHO Prequalification programme. A linezolid 150mg dispersible tablet is fully developed and could be an alternative to the expensive Pfizer oral suspension that has an unstable supply.

After years of advocacy towards manufacturers, these are positive developments. Nevertheless, further efforts are still needed to ensure development of a full paediatric MDR-TB regimen comprised entirely of formulations adapted for children's needs.

Paediatric formulations of bedaquiline and delamanid are expected following the conclusion of on-going trials. An Otsuka trial studying delamanid pharmacokinetics in children will provide needed information in this population. Other pharmaceutical companies should do the same.

### **Companion medicines: registration must be prioritized**

Countries should have access to all WHO-recommended MDR-TB medicines, including 'repurposed' medicines that have shown to provide value in TB treatment. Although developed and approved for use under other conditions, these companion drugs are needed to maximize the effectiveness of MDR-TB treatment and prevent resistance to newer MDR-TB medicines, such as bedaquiline and delamanid. Repurposed medicines such as clofazimine should have a TB indication and be registered with a TB indication in high-burden countries as a priority. This will help in enabling repurposed medicines to be included in national TB guidelines and prescribed by TB physicians, and will also help to ensure long-term supply through standard importation procedures.

Clofazimine was added to the WHO Essential Medicines List (EML) for use in TB treatment in adults and children in March 2017. It is important that countries update national EML and national guidelines accordingly. Based on June 2016 updates to WHO MDR-TB treatment guidelines, clofazimine plays a key role in shorter MDR-TB treatment regimens. Clofazimine's originator, Novartis, is currently the only quality-assured manufacturer of the drug. Two generic versions will potentially be available within the next two years, creating a welcome opportunity for necessary price reductions and to meet growing demand for the drug with increased implementation of shorter MDR-TB treatment regimens. Despite their investment in production capacity, it is unlikely that Novartis alone will be able to meet expected worldwide demand for clofazimine.

Linezolid was also added to the WHO EML for use in TB treatments in adults and children in April 2015. Based on June 2016 updates to WHO MDR-TB treatment guidelines, linezolid is considered as an important medicine to build effective regimens for the treatment of MDR-TB and XDR-TB, in association with bedaquiline and/or delamanid. The price of linezolid fell by 70% in 2016 thanks to enhanced competition among the four generic companies that manufacture it in addition to Pfizer, the originator company.

## **Spotlight on ongoing MDR-TB clinical trials and medicines pipeline**

### **Ongoing MDR-TB clinical trials**

Several trials are currently investigating the use of shortened MDR-TB treatment regimens as well as use of the newer drugs bedaquiline and delamanid; however, the earliest results are not expected until 2018.<sup>33</sup> MSF is involved in two clinical trials – endTB and TB PRACTECAL – seeking optimal treatment regimens for MDR-TB using the newer drugs.

#### **endTB**

Expand New Drug Markets for TB (endTB)<sup>34</sup> is a partnership between Partners in Health, MSF, Interactive Research & Development and financial partner Unitaid covering 17 countries (Armenia, Bangladesh, Belarus, Democratic People's Republic of Korea, Ethiopia, Georgia, Haiti, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa and Vietnam). Across all 17 countries, endTB treats and closely monitors a large cohort of 2,600 patients receiving regimens containing the newer TB drugs bedaquiline and/or delamanid in order to establish an evidence base for broader, safe use of new MDR-TB drugs and to address country-level barriers to enable access to new TB drugs.

A phase III randomised controlled clinical trial will be conducted in a total of 6 of the above countries (Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru and South Africa) to find shorter, simpler, less toxic, oral, more tolerable and more effective treatments for MDR-TB using the newer drugs. A total of 750 participants will be enrolled in the trial and each experimental regimen contains at least one new drug in combination with up to 4 companion drugs. The newer drugs are being combined with other oral TB drugs such as clofazimine, linezolid, fluoroquinolones and pyrazinamide. The first patient in the trial started treatment in Georgia in March 2017 and 25 patients have been enrolled to date in Georgia, Kazakhstan and Peru. The trial is scheduled to conclude in 2020.

#### **TB PRACTECAL**

TB PRACTECAL<sup>35</sup> is a phase II/III randomised controlled clinical trial with the aim of finding short (6-month), tolerable and effective treatment regimens for people with MDR-TB. The trial is sponsored and run by MSF and is supported by the London School of Hygiene and Tropical Medicine as well as other leaders in medical research. The trial is conducted in two stages, scheduled to be completed in 2018 and 2021. In the first stage, a phase II trial compares 3 different regimens containing the newer drugs bedaquiline and pretomanid, given in combination with companion drugs linezolid, clofazimine and moxifloxacin. In the second stage, a phase III trial will continue to test the two most successful regimens emerging from the phase II trial compared to the locally accepted WHO-recommended standard treatment for MDR-TB and XDR-TB.

The trial began on 17 January 2017 when the first patient started on treatment in Uzbekistan. As of 31 August 2017, 38 participants were enrolled in Uzbekistan. They are the first of 630 patients to be recruited from Uzbekistan, Belarus and South Africa. The other trial sites are due to start by the end of 2017. In addition to the development of shorter regimens, the trial also aims to contribute to global access to the newly identified treatment regimen, if successful, through its adoption into national protocols and global policies and guidelines.

## **Other clinical trials**

The TB Union STREAM 1 trial compares the WHO-approved shorter 9-month regimen for treatment of uncomplicated MDR-TB against the standard 24-month WHO MDR-TB regimen. STREAM 1 has completed enrolment and results are expected in 2018.

The TB Union STREAM 2 trial is comparing the two regimens studied in STREAM 1 against a 6-month bedaquiline-containing regimen and a 9-month bedaquiline-containing regimen. STREAM 2 is currently enrolling and results are expected in 2021.<sup>36</sup>

The NeXT trial, sponsored by the University of Cape Town in South Africa, is also looking at a 6- to 9-month, injection-free regimen containing bedaquiline. Results are expected in 2019.<sup>37</sup>

The NiX-TB trial, led by TB Alliance, is studying a 6-month regimen containing bedaquiline, linezolid and pretomanid (BPaL) that has demonstrated very promising outcomes so far. After experiencing severe adverse reactions related to the high dose of linezolid, another arm – Ze-NIX – was added to the trial to study lower linezolid doses. Results are expected in 2021.<sup>38</sup>

## **MDR-TB medicines pipeline**

### **Pretomanid (PA-824)**

In the same family as delamanid, pretomanid is a nitroimidazole – a class of anti-bacterial agents. Developed by TB Alliance, pretomanid has the potential to be a cornerstone of future TB and MDR-TB treatment regimens but is still only available for use in clinical trials. It has been used in several trial regimens and clinical trials but there are currently no indications of pricing or mechanisms for access post-trial.<sup>39</sup>

### **Sutezolid**

Sutezolid is in the same family as linezolid, and has the potential to have a better safety profile. Nearly five years after showing promise in phase IIa, sutezolid is still awaiting entry into phase IIb trials. In 2012, Pfizer reported the results of its first study of sutezolid in TB patients, which showed the drug to be safe and active against TB in South African participants with DS-TB – with and without HIV, but not on antiretroviral treatment.<sup>40</sup>

A study by the AIDS Clinical Trial Group (A5289) is under development and currently features sutezolid replacing ethambutol in a trial to evaluate the pharmacokinetics, safety and initial efficacy of sutezolid DS-TB. It would determine an ideal dose for sutezolid and also evaluate interactions between rifamycins and sutezolid and its main metabolite. If study A5289 is approved for implementation, it will trigger the long-awaited entry of sutezolid into phase IIb.<sup>41</sup>

The primary patent on sutezolid expired in 2014, but Pfizer, Sequella and Johns Hopkins University still hold secondary patents and clinical data on the drug.<sup>42</sup> In January 2017, Johns Hopkins, holder of several such patents, signed a voluntary license with the Medicines Patent Pool, whose mandate is to increase innovation and access to drugs through voluntary licensing. The license will enable open, non-exclusive licenses with multiple drug developers to conduct research and develop drug combinations that include sutezolid.<sup>42</sup> The license is royalty-free, signed exclusively with the Medicines Patent Pool (which can thereafter issue sub-licenses), and covers all countries that currently have patents issued or pending for a combination therapy comprising sutezolid. One concern with the license agreement is that it allows a sub-licensee to charge higher, tiered prices in high-income countries, with the exception of Bulgaria, Estonia, Latvia, Lithuania and Russia. Following this licence, on March 2017 2017, World TB Day, the TB Alliance and the Medicines Patent Pool announced a licensing agreement for the clinical development of sutezolid, pertaining to the development of sutezolid in combination with other TB drugs.<sup>43</sup>

## Annex: Evolution of GDF price ranges for MDR-TB medicines since 2015 and available quality-assured sources

Prices are presented in US\$ and correspond to the price of one unit (tablet, capsule, etc.). Percentages indicate price evolution of the lowest available GDF price (comparing 2016 to 2015 and 2017 to 2016).

Drug	GDF indicated prices*			Quality assured MDR-TB medicines available on the market†								
	In 2015	In May 2016	In Sep 2017	Bros	Medo-chemie	Pharmatex	Vianex	Pharma-then Hellas				
Amikacin												
500mg/2ml solution for injection	0.678-0.805	0.635-0.674 -6%	0.617-0.635 -3%	X	X	X	X	X				
<b>Kanamycin</b>												
0.5g powder for injection	--	0.850	0.850	X	--	--	X					
1g powder for injection	1.000-1.721	2.250 +125%	2.250	X	--	X	X					
1g/4ml solution for injection	2.560	2.360 -9%	2.360	--	X	--	--					
<b>Capreomycin</b>												
0.5g powder for injection	--	2.990	2.990						King Pharmaceuticals			
1g powder for injection	3.800-4.700	3.600-4.700 -5%	3.600-4.700	X	X	X	X	X	X			
<b>Moxifloxacin</b>												
400mg tablet	0.437-0.540	0.310-0.386 -29%	0.310-0.386	X	X	X	X	X	X	Bayer	Mylan	
<b>Levofloxacin</b>												
250mg tablet	0.033-0.055	0.028-0.038 -15%	0.028-0.038	X	X	X	X	X	X	Denk Pharma	Medo-chemie	HEC
500mg tablet	0.059-0.097	0.049-0.064 -17%	0.049-0.064	X	X	X	X	X	X	X	X	X
750mg tablet	0.100	0.100	0.100	X	--	X	X	--	--	--	--	--
<b>Ethionamide</b>												
125mg tablet	--	0.100	0.100									
250mg tablet	0.062-0.080	0.064-0.067	0.062-0.077 -3%	X	X	X	X					
<b>Prothionamide</b>												
250mg tablet	0.130-0.178	0.059-0.155 -56%	0.085-0.183 +44%	X	X	X	X					
<b>Cycloserine</b>												
250mg capsule	0.187-0.330	0.187-0.288	0.268-0.288 +43%	X	X	X	X	X				
<b>Terizidone</b>												
250mg capsule	1.588-1.666	1.666-3.490 +5%	1.745 +4%	X								
<b>PAS</b>												
4g sachet	1.333	1.333	1.333	X								

Drug	GDF indicated prices*			Quality assured MDR-TB medicines available on the market†								
	In 2015	In May 2016	In Sep 2017	Macleods	Olainfarm							
<b>PAS-sodium</b>												
60% w/w granules – 9.2g sachet	1.690	1.240 <i>-27%</i>	1.240	X	--							
60% w/w granules – 100g jar	18.360	--	--	X	--							
Powder for oral solution – 5.52g sachet	1.370	1.350	1.350	--	X							
<b>Clofazimine</b>				Novartis								
50mg soft-gel capsule	0.547-0.713	0.547	--	X								
100mg soft-gel capsule	1.095-1.267	1.095	0.982 <i>-10%</i>	X								
<b>Linezolid</b>				Hetero	Macleods	Pfizer	Teva	Dr Reddy's	Pharmacia			
600mg tablet	5.350-5.480	1.379-1.521 <i>-73%</i>	1.379-1.521	X	X	X	X	X	X			
<b>Imipenem/cilastatine</b>				Demo	Sun Pharma	Pan-pharma	Fresenius Kabi	Labatec				
500mg/500mg, btl. powder for infusion	--	3.068 – 10.220	3.500 <i>+14%</i>	X	X	X	X	X				
<b>Bedaquiline</b>				Janssen								
100mg tablet	0.00 <i>Donation</i>	0.00 <i>Donation</i>	0.00 <i>Donation</i>	X								
<b>Delamanid</b>				Otsuka								
50mg film-coated tablet	2.530	2.530	2.530	X								

\* <http://www.stoptb.org/gdf/drugsupply/pc2.asp?CLevel=1&CParent=1>

† Companies with an 'X' are currently producing quality-assured versions of each MDR-TB medicine identified. All known SRA and/or PQ approved and/or Expert Review Panel temporary approved sources as per the Global Fund:  
<https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/>

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MSF Access Campaign  
Médecins Sans Frontières, Rue de Lausanne 78  
CP 116, CH-1211 Geneva 21, Switzerland

**T** + 41 (0) 22 849 84 05  
**F** + 41 (0) 22 849 84 04  
**E** [access@msf.org](mailto:access@msf.org) / [www.msf.org](http://www.msf.org)  
 [twitter.com/MSF\\_access](https://twitter.com/MSF_access)  
 [facebook.com/MSFaccess](https://facebook.com/MSFaccess)

