MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN
DR-TB DRUGS UNDER THE MICROSCOPE
5TH EDITION (ABRIDGED)

DESPITE SOME POSITIVE DEVELOPMENTS, ACCESS TO SAFE AND EFFECTIVE TREATMENT FOR DRUG-RESISTANT TB REMAINS POOR

Although tuberculosis (TB) is the number-one infectious disease killer[1] and one of the top ten causes of mortality worldwide, the global response to TB remains off track.[2] The interim 2020 targets set by the World Health Organization (WHO) End TB Strategy – to reduce new TB infections by 20%, reduce TB deaths by 35%, and eliminate catastrophic costs of treatment for families – won't be reached unless there is a dramatic increase in the pace of the global TB response.

The TB epidemic is exacerbated by the rise of drug-resistant TB (DR-TB), flagged by WHO as a global emergency in 2014 and again in 2017. An estimated 558,000 people fell ill with drug-resistant forms of TB in 2017 – but only 25% of them were started on treatment.[1]

The standard DR-TB treatment regimens used by most countries today have a high pill burden, long treatment duration (around two years), severe side effects, and poor treatment outcomes. These regimens only cure 55% of people with multidrug-resistant TB (MDR-TB), and only 34% of people with extensively drug-resistant TB (XDR-TB).[1]

While significant and growing evidence show that two newer drugs, bedaquiline and delamanid, significantly improve treatment outcomes and reduce side effects, these medicines remained inaccessible to nearly 90%* of people eligible to receive them in 2017, based on WHO recommendations at the time. Many factors, including high prices and regulatory challenges as well as slowness in gathering enough clinical evidence to update WHO and national guidelines, have certainly cost lives.

Meeting the global TB goals to reduce TB incidence and deaths requires not only broad implementation and effective use of the current tools available to prevent, diagnose and treat TB, but also the development of better clinical tools, from point-of-care rapid diagnostic and drug-resistance tests, to safer, shorter and more effective treatment regimens that are easier to administer.

Both adequate funding and critical changes in the way TB research and development (R&D) is done are needed. This includes collaborative approaches such as sharing and licensing of clinical trial data and drug molecules, which would address the specific access needs of people with TB and bring the next generation of effective TB drugs and regimens to them as quickly as possible.

STATE OF THE EPIDEMIC IN 2017

- Number one infectious disease killer worldwide
- 1.6 million deaths in 2017
- 10 million people with newly active TB in 2017
- 36% of people with active TB remain undiagnosed or unreported
- Only 25% of people with drug-resistant TB have received treatment

Source: WHO Global TB Report 2018[1]

This report chronicles the changing landscape of available treatments for DR-TB, outlines the key barriers to accessing the most effective treatments, and makes recommendations for action that can improve TB care on a global scale.

© Sydelle Willow Smith

Simbongile Xesha at her local primary care clinic in Khayelitsha, Western Cape, South Africa. Her XDR-TB treatment included the newer TB drug bedaquiline, found to significantly improve treatment outcomes and reduce side effects.

* Based on a conservative estimate that globally 33% of people diagnosed and put on treatment for MDR- and RR-TB could have been treated with bedaquiline or delamanid, according to WHO guidelines at the time.

ACCESS CAMPAIGN
MÉDECINS SANS FRONTIÈRES

endTB

KEY FINDINGS

Our analysis highlights some positive developments in the DR-TB treatment landscape: prices of some medicines have come down; more paediatric formulations to treat children with DR-TB are now available; and a healthier market dynamic for TB medicines has evolved with the increase in the number of quality-assured suppliers.

Most importantly, in August 2018, WHO revised its recommendations for treatment of MDR-TB and rifampicin-resistant TB (RR-TB) to all-oral regimens, prioritising the use of bedaquiline as now one of three core drugs to be used in all MDR-TB treatment regimens for all patients, and minimising the use of second-line injectable aminoglycosides, which often cause pain, distress and serious side effects. This recommendation more than doubles the number of people for whom bedaquiline-containing regimens are recommended. Previously, the use of bedaquiline was limited to when it was otherwise not possible to compose an effective regimen with older TB drugs.

While positive, these developments should be viewed in the context of the persistent and yawning testing and treatment gap for people with MDR-TB: in 2017 only 29% of people estimated with MDR-TB were diagnosed and just 25% of the estimated MDR-TB cases were treated.[1]

The fragile gains in price reductions and additional quality-assured suppliers seen over the past 10 years are at risk. The necessary and welcome switch to mostly injectable-free treatment regimens using bedaquiline, linezolid and fluoroquinolones as core drugs will certainly increase the price of treatment regimens unless a concerted effort is made to prioritise the affordability of these effective drugs. In addition, as countries lose financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria, and/or switch to national procurement systems, a re-fragmentation of the market for DR-TB medicines and slower introduction of newer regimens and drugs could result.

To accelerate the TB response, thereby ensuring as many people as possible gain access to optimal treatment, governments must take rapid action to implement the new WHO DR-TB treatment recommendations; drug companies must contribute their part by ensuring local registration, wide availability, and affordability of medicines, with a target price of no more than US$500 per person for a full DR-TB regimen; and the Global Fund and other donors must offer financial and technical support to countries in upgrading national protocols and rolling out improved treatment regimens.

MSF AND TB

As the largest non-governmental provider of DR-TB treatment, Médecins Sans Frontières (MSF) is regularly confronted with the deadly effects of numerous and long-standing barriers to improving TB care. MSF supports national TB programmes in 29 countries and treated 22,100 people in 2017, including 3,600 people with DR-TB.[3]

MSF strives to implement optimal TB diagnostic tools, treatments and models of care in order to give people the best chance to survive drug-resistant forms of the disease. MSF is conducting research on new DR-TB treatments through two clinical trials, endTB[4] and PRACTECAL[5], and through other implementation research.

Following years of unsuccessful treatment, this 18-year-old patient (name withheld) was referred to MSF's clinic in Mumbai, India, where she was diagnosed with XDR-TB and eventually gained access to the newer TB drug delamanid.

© Atul Loke

TREATMENT LANDSCAPE:
Slow progress towards more optimal regimens

UPDATE #1: WHO RECOMMENDS IMPROVED DR-TB TREATMENT

In August 2018, WHO announced a set of new DR-TB treatment recommendations that will be included in its updated MDR-TB and RR-TB treatment guidelines scheduled for release in November 2018.[6] The changes are based on an assessment of the latest evidence on individual drug effectiveness and safety gathered from programmes and researchers around the globe.

The new WHO recommendations prioritise the use of several oral drugs, including the newer drug bedaquiline, and minimise the use of injectable aminoglycosides that cause deafness and other severe side effects. This new combination of drugs for MDR-TB and RR-TB in an 18- to 20-month treatment regimen are recommended to improve treatment outcomes, decrease mortality, significantly reduce side effects, and improve quality of life.

WHO is urging countries to take immediate steps towards implementation of the new treatment protocols, including adapting national protocols, procuring necessary drug stocks, and introducing specific patient monitoring. More than ever, updated diagnostic algorithms and accurate drug resistance testing are vital to ensure clinicians can rapidly identify and prescribe the most appropriate DR-TB treatment regimen for each individual with close monitoring of patient safety and treatment outcomes.

While the TB community awaits more clinical trial data on the optimal duration and composition of treatment regimens, evidence from observational cohorts following active drug safety monitoring (aDSM) principles will continue to play an important role in WHO guideline development guiding improvements in DR-TB care. Results from the clinical trials currently underway will only be available after 2020 (see Box "Snapshot of key clinical trials for new DR-TB regimens", page 5).

WHO'S NEW RECOMMENDATIONS FOR MDR-TB AND RR-TB TREATMENT

Key points from the rapid communication from WHO in August 2018,[6] which outlines the planned changes to MDR-TB and RR-TB treatment guidelines expected to be published in November 2018, include the following:

Grouping of medicines:

- The core drugs to treat MDR-TB and RR-TB are levofloxacin/moxifloxacin, linezolid and bedaquiline (Group A core drugs), as well as clofazimine and cycloserine (Group B drugs).

- The injectable aminoglycosides, kanamycin and capreomycin, are no longer recommended given increased risk of treatment failure and relapse associated with their use in longer MDR-TB regimens.

- Amikacin remains the only main injectable aminoglycoside recommended and is classified as a Group C[a] drug, which are to be used to complete regimens when drugs from Group A and B cannot be used. Amikacin should replace kanamycin in the standardised shorter MDR-TB regimen (WHO 2016), [b,7] though drug-resistance testing is mandatory prior to use of this regimen.

- For now, delamanid is listed as a Group C medicine; additional evidence from raw data of the Otsuka delamanid 213 study could change this in the near future.[c]

Treatment regimens:

- Standard regimens are 18 to 20 months and must contain five effective medicines from Group A and B, completed with drugs from group C if necessary.

- Shorter regimens, including the standardised shorter MDR-TB regimen (WHO 2016), are recommended only for people who do not have resistance to any of the drugs in this regimen (fluoroquinolones, amikacin, ethionamide, pyrazinamide, ethambutol).

- Treatment options for MDR-TB are increasingly more individualised. Three signals are clear from the current scientific evidence assessment:
  - All-oral treatment regimens are feasible, effective, and preferable for most patients.
  - Drug resistance must be excluded (at least to drugs for which rapid molecular tests are available) before starting patients on treatment, especially for the standardised shorter MDR-TB regimen (WHO 2016).
  - Close monitoring of patient safety and treatment response is needed, and a low threshold should be used for switching non-responding patients or those experiencing drug intolerance to alternative medicines and/or new regimens based on the regrouping of agents.

Upscaling of necessary diagnostic testing and patient monitoring:

- Effective patient monitoring according to WHO aDSM principles, including:
  - Routine biochemistry and haematology testing
  - Capacity to conduct audiometry and electrocardiograms
- Accurate drug-resistance testing and use of specific diagnostic tools and protocols, including:
  - Transition to Xpert MTB/RIF Ultra for initial diagnosis of TB and detection of rifampicin resistance for both pulmonary and extrapulmonary TB
  - Capacity to accurately attain drug-resistance profiles using recommended phenotypic and genotypic testing (including sequencing) for all relevant drugs

[a] Group C drugs: ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, *p*-aminosalicylic acid

[b] The standardised shorter MDR-TB regimen refers to a course of treatment for MDR/RR-TB lasting nine to twelve months, which is largely standardised, and whose composition and duration follows closely the one for which there is documented evidence from different settings. The shorter MDR-TB treatment regimens were standardised in content and duration and split into two distinct parts. First, an intensive phase of four months (extended to six months in case of lack of sputum smear conversion) was given including the following drugs: gatifloxacin (or moxifloxacin), kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol. This was followed by a continuation phase of five months with the following drugs: gatifloxacin (or moxifloxacin), clofazimine, ethambutol, and pyrazinamide (prothionamide was kept in the continuation phase in earlier studies).

[c] Additional data on delamanid was unavailable during the initial evidence review and is currently under review, hence the role of delamanid will likely be clarified in the November 2018 WHO guidelines.

UPDATE #2: BUILDING THE EVIDENCE FOR OPTIMAL USE OF NEW TB DRUGS

A number of research initiatives are currently ongoing to identify which drug combinations result in more effective, less toxic, all-oral regimens. These trials incorporate the newer drugs bedaquiline and delamanid, as well as other drugs emerging from the pipeline, such as pretomanid. However, progress is slow, considering that bedaquiline and delamanid were approved more than five years ago.

Bedaquiline and delamanid provide two clear examples of how the way pharmaceutical research and development (R&D) is conducted fails people with TB. These new drugs were developed and brought to market in isolation, each as an add-on to the long and poorly tolerated DR-TB standard regimen. While individual add-ons can be expected to improve efficacy, they are not designed nor tested to do what we really need to improve DR-TB treatment outcomes: shorter, better-tolerated, more effective regimens, combining new drugs in optimal ways with other WHO-recommended drugs, including replacing some of the less effective or more toxic drugs with new drugs. This requires a very different approach to drug development, one that focuses on designing optimal regimens that maximise patient benefit from the start, rather than assessing individual add-on drugs.

The companies that developed these latest drugs, Johnson & Johnson (J&J) for bedaquiline and Otsuka for delamanid, obtained marketing authorisation based on phase II clinical trial safety and efficacy data suggesting increased efficacy as an add-on, but left the work of testing these drugs in optimal regimens to others. Although these companies hold the patents and control access to these drugs, other actors, including MSF, have over the past years confirmed the clinical benefit of these drugs, in particular bedaquiline, in clinical practice, and are currently conducting the clinical trials that are expected to establish how to best use these drugs in shorter, better-tolerated, more effective regimens. This example illustrates how commercial TB R&D is disconnected from DR-TB medical needs and is driven mainly by marketing authorisation goals.

MSF is participating in two of the several clinical trials underway, endTB and PRACTECAL, that are evaluating the optimal use of these and other new medicines in shorter DR-TB regimens (see Box, "Snapshot of key clinical trials for new DR-TB regimens", page 5). The time required to complete ongoing randomised, controlled clinical trials of regimens with bedaquiline and delamanid means that the earliest results are not expected before 2021; so it will be another two to three years before the evidence from these trials can inform refinements or updates to the WHO treatment recommendations announced in August 2018.

In the meantime, as reflected by WHO's decision to issue new treatment recommendations, a strong and growing body of observational evidence is already showing that safety, efficacy and clinical outcomes are significantly better for people who have been treated with regimens containing bedaquiline and repurposed[d] drugs such as linezolid.

MSF is contributing to this body of evidence: across MSF projects in 14 countries, some of which are endTB observational study sites, more than 2,000 people have been treated with the newer drugs – 633 with delamanid, 1,530 with bedaquiline, and 227 with a combination of both medicines – as of September 2018.

According to interim treatment results from the endTB observational study,[8] which were shared with the WHO Guideline Development Group for assessment, delamanid and bedaquiline appear to be safer to use than some commonly used DR-TB medicines that have serious side effects, including second-line injectable aminoglycosides and linezolid. The endTB observational study interim analysis provided data on the six-month treatment response of the world's largest prospective cohort of patients receiving bedaquiline or delamanid, reporting on 1,244 people enrolled at sites across 17 countries by MSF, Partners in Health (PIH) and Interactive Research and Development (IRD). Adverse events possibly caused by the injectable aminoglycosides were common in the endTB cohort: 36% of patients who received an injectable aminoglycoside experienced at least one injectable-related toxicity at clinically relevant levels (hearing loss, acute renal failure, or hypokalaemia/hypomagnesemia). Toxicity commonly associated with linezolid was less common but affected important numbers of patients, with peripheral neuropathy (9%), myelosuppression (4%), and optic neuritis (2%).

The Ministry of Health in South Africa recently announced it would remove second-line injectable aminoglycosides from standard DR-TB treatment regimens and replace them with bedaquiline.[9] This decision comes after analysis of programmatic data found that patients with RR-TB treated with bedaquiline-based regimens had a significant reduction in mortality compared to those treated without bedaquiline.[10]

© Sydelle Willow Smith

Simphiwe Zwide was prescribed treatment for his XDR-TB that included both newer TB drugs, bedaquiline and delamanid. These medicines were inaccessible to nearly 90% of people eligible for them in 2017, based on WHO recommendations at the time.

---

[d] Repurposed medicines are compounds developed for other indications (e.g. leprosy for clofazimine) which have shown, or are thought to be, effective against TB.

Interim results from the endTB observational study also showed 79% culture conversion (an important marker indicating a patient is responding to treatment, or is recovering from TB) at six months in patients treated with regimens where delamanid was included (among 174 people). Conversion probabilities were similar for those patients with XDR-TB and those with XDR-TB or pre-XDR-TB with fluoroquinolone resistance, who also culture-converted after six months. The high rate of culture conversion is consistent with results reported by other observational studies.[11,12,13] This and other evidence currently under review by the WHO may help build the case for including delamanid in standard DR-TB regimens in the future, possibly as soon as November 2018, when updated WHO treatment guidelines are expected. In the endTB observational study, no statistically significant difference in culture conversion within six months was observed between patients who received delamanid- and bedaquiline-containing regimens.

In accordance with WHO's 2016 interim guidelines for the newer drugs, people in the endTB observational study who received bedaquiline or delamanid were monitored for a lengthened QT[e] interval,[14] which is a cardiovascular risk factor for sudden death. QT interval prolongation was found to be much less frequent than expected and was not associated with use of delamanid or bedaquiline, nor with HIV status.[8]

Today, data are scarce on many important aspects of how to use these important new drugs to achieve optimal results in patients, and this limits the extent to which WHO is able to give detailed advice to countries on how best to use them. However, data are starting to emerge as clinicians, encouraged by the results they see in their patients, expand the use of bedaquiline and delamanid to wider cohorts of patients.

A recent study by Ferlazzo et al[15] has contributed valuable evidence supporting the safety and effectiveness of combining bedaquiline and delamanid, in a particularly difficult-to-treat group of patients, with 74% culture conversion among patients who were culture-positive at baseline. Safety-wise, none of the 28 patients had a QTcF interval more than 500 ms, and no cardiac events were reported.

In the endTB observational study, over one-third of patients receive more than the standard six months of bedaquiline or delamanid[16] to ensure sufficient effective drugs in their treatment regimen for the entire duration. Guglielmetti et al[17] have published evidence showing excellent results and no additional safety concerns when bedaquiline is used for as long as needed, with most patients receiving it for more than six months. The standard six-month treatment for bedaquiline and delamanid relates to the original labelling approved on the basis of the treatment duration tested in clinical trials for each medicine, respectively by the US Food and Drug Administration in 2012 and the European Medicines Agency in 2014. As these new drugs are used more widely and in a broader population of DR-TB patients compared to clinical trials, evidence continues to accumulate on the best ways to use them, including evidence on the extension of the duration of their use.

Pretomanid, the latest new drug candidate, is being developed by the non-profit product development partnership TB Alliance. Pretomanid is being assessed as part of a new regimen for treatment of XDR-TB in the Nix-TB and ZeNix trials.[18,19] The trials aim to evaluate an all-oral, six- to nine-month regimen combining bedaquiline, linezolid and pretomanid. The initial Nix-TB trial showed promising culture-conversion results (74% among 34 people with XDR-TB who completed six months of treatment) but was stopped early for several reasons,[20] including high levels of toxicity associated with the high dose of linezolid.[21] The follow-up trial ZeNix is assessing more optimal doses of linezolid. TB Alliance has also initiated a third trial, SimpliciTB,[22,23] evaluating whether a new four-drug regimen combining bedaquiline, pretomanid, moxifloxacin and pyrazinamide can treat most types of TB, including drug-susceptible TB and MDR-TB, more quickly and effectively than currently available treatments.

SNAPSHOT OF KEY CLINICAL TRIALS FOR NEW DR-TB REGIMENS

endTB: randomised controlled trial comparing five new, all-oral, nine-month MDR-TB regimens to the WHO-recommended standard of care. Five experimental regimens including bedaquiline and/or delamanid with various combinations of clofazimine, linezolid, moxifloxacin or levofloxacin, and pyrazinamide. Outcomes expected by 2022. Sponsor: MSF[4,24]

NEXT: randomised controlled trial of a six- to nine-month injection-free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high-dose isoniazid, and pyrazinamide comparing with South African standard regimen. Currently enrolling participants in South Africa. Outcomes expected by 2020. Sponsor: University of Cape Town[25]

PRACTECAL: randomised controlled phase II-III trial evaluating six-month MDR-TB treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed TB medicines. Outcomes expected by 2021. Sponsor: MSF[5,26]

STREAM II: first phase III clinical trial to test the effectiveness of bedaquiline within an all-oral, nine-month MDR-TB treatment regimen. Outcomes expected by 2023. Sponsor: The Union/IUATLD[27,28,29]

ZeNix: non-randomised uncontrolled trial testing a three-drug XDR-TB regimen consisting of bedaquiline, pretomanid and linezolid in six- to nine-month regimen. Outcomes expected by 2022. Sponsor: TB Alliance[19,30]   (see also former Nix-TB trial[18,20,21])

---

e The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave. Thus, it is the electrocardiographic manifestation of ventricular depolarisation and repolarisation.

UPDATE #3: FINALLY A BIT OF GOOD NEWS FOR CHILDREN WITH DR-TB

In the past three years, paediatric formulations for six critical DR-TB medicines (cycloserine, ethionamide, isoniazid, levofloxacin, moxifloxacin and pyrazinamide) have been either WHO-prequalified or approved as quality-assured through the Expert Review Panel (ERP) process managed by the Stop TB Partnership's Global Drug Facility (GDF) and the Global Fund. A full list of the paediatric formulations available, including doses and manufacturer names, can be viewed in the Online Supplement available at msfaccess.org/utm5.

All of these paediatric formulations will be available from GDF starting in Q4 2018. To help catalyse rapid adoption of the new medicines to treat children, Stop TB Partnership/GDF has funded the Sentinel Project on Paediatric Drug-Resistant Tuberculosis[31] to promote the use of these paediatric formulations in 18 countries, including providing technical support to countries in adapting their treatment guidelines and in implementing appropriate medical tools to more effectively treat DR-TB in children. This project will enable GDF to purchase initial medicine stocks such that countries are able to build complete regimens using paediatric formulations.

Unfortunately, the good news on the number of specific formulations for children available is tempered by the ongoing difficulties accessing existing paediatric formulations for important DR-TB drugs, such as linezolid and delamanid, as well as lack of formulations and data on how to use other drugs such as bedaquiline.

Linezolid, an old drug with neurological side effects, is now classified as a core medicine in building DR-TB regimens. A paediatric syrup is manufactured by Pfizer, but major barriers exist in accessing this important drug. First, at US$318 per bottle, its price is out of reach for most TB programmes. Second, an irregular production cycle due to low global demand means that supply is not assured. A second supplier, Macleods, is developing a dispersible tablet that is expected to be submitted to the ERP by Q4 2018.

WHO's interim policy guidance on delamanid recommends it for use in children as young as six years old,[32] in the form of the 50mg tablet adult formulation. Currently, more paediatric data are available on the safety and dosing of delamanid compared to some other DR-TB medicines used in children, such as cycloserine and clofazimine. However, the WHO interim guidance does not make a recommendation of delamanid use in children younger than six years old, citing lack of available data.[32] The 50mg tablet adult formulation was added to the WHO Essential Medicines List for children over six years of age in 2017;[33] however, no adapted product is currently marketed for children younger than six.

For children younger than six, Otsuka has signed a memorandum of understanding (MOU) with the Medicines Patent Pool on paediatric formulations containing delamanid. But to date, no company has stepped up to manufacture, register and supply this formulation, since the way this MOU was designed fragments the market between adult and paediatric formulations, de-incentivising alternative suppliers from producing and registering for the cohort of children under age 6.[34]

In parallel, Otsuka and Mylan, its commercial partner for the registration and distribution of the adult formulation of delamanid in certain countries,[f] are negotiating a bilateral deal to initiate the production of dispersible tablets. Otsuka and Mylan should transparently make the terms and conditions of the agreement available to procurers, treatment providers and governments, and should specify which company will manufacture, register, market and distribute the paediatric dispersible tablet in different high-burden countries.

J&J's paediatric trial for bedaquiline, C211, is still ongoing. Pharmacokinetics and six-month safety data from Cohort 1 (12-17 years of age) will be presented at The Union conference in October 2018. Cohort 2 (5-11 years of age) is now fully enrolled. As additional data become available, it is imperative to swiftly update label information and WHO recommendations with applicable age indications. Today, no paediatric formulation of bedaquiline is available, although recent evidence points to the possibility of dissolving adult doses to produce a child-friendly solution, which may be useful as an interim approach.[35]

The number of children and adolescents with DR-TB who have access to MDR-TB treatment using new drugs remains very low, in both MSF-supported projects and internationally. As of June 2018, MSF has treated at least 38 children and adolescents under 18 years of age with bedaquiline, and 61 with delamanid. Internationally, an estimated 25,000 new cases of MDR-TB occur each year among children and adolescents younger than 15 years of age, and less than 2,500 (10%) of them are diagnosed and put on treatment.[36,37] Despite evidence that treatment can be effective and well-tolerated in this age group, many are not diagnosed, treated, or given access to newer drugs.

© Maxime Fossat

An MSF health promoter provides follow-up care at the home of a nine-year-old girl (name withheld) being treated for TB in Osh, Kyrgyzstan.

---

f Afghanistan, Bangladesh, Brazil, Cambodia, Democratic Republic of Congo, Ethiopia, India, Kenya, Mozambique, Nigeria, Pakistan, South Africa, Tanzania, Uganda and Zimbabwe, plus all countries where Otsuka has no commercial presence.

ACCESS TO TREATMENT:
Prices drop for some older DR-TB medicines, but high prices and erratic local registration still pose significant barriers

THREAT #1: HIGH PRICES OF DR-TB MEDICINES

MSF has advocated that the price of a full DR-TB regimen should be no more than US$500 per person in order to facilitate broad scale-up of treatment. This price should be available for at least all low- and middle-income countries and high TB burden countries. Some progress towards this goal has been made, but most regimens – including in particular those newly recommended by WHO – are still far too expensive.

Countries eligible to purchase medicines through the GDF, the largest supplier of quality-assured TB medicines, have access to some of the lowest prices available for TB medicines. Over the past six years, GDF prices for conventional DR-TB regimens (those recommended by WHO until the latest August 2018 announcement) have significantly dropped – by up to 200% for some regimens (see Table 1, "DR-TB regimen pricing, 2012-2018", page 8).

Since WHO recommended a standardised shortened DR-TB regimen for some patients in 2016,[7] its price has dropped more than 30% to US$488 per person. However, the new WHO treatment recommendations announced in August 2018 replace kanamycin with amikacin, which costs twice as much; the shortened regimen price will thus increase to US$572.

Prices have fallen significantly for older medicines for which high prices have been a persistent barrier in the past (see Table 2, "Pricing trends for key DR-TB medicines", page 8). These decreases were gained thanks to healthier competition across more numerous generics manufacturers stimulated by GDF in supporting countries to improve their DR-TB drug forecasts and in setting up regular international tenders where only suppliers of quality-assured medicines compete. Two of these drugs, moxifloxacin and linezolid, are now considered core DR-TB medicines, alongside bedaquiline, in the new WHO DR-TB recommendations; moxifloxacin and linezolid are also being tested in some clinical trials. Despite a significant drop in the price for linezolid at GDF (-451%), this key DR-TB medicine remains unaffordable for most countries.

High prices persist for four other important DR-TB medicines used in WHO-recommended regimens: bedaquiline, delamanid, clofazimine and imipenem-cilastatin. Regimens containing the newer drugs bedaquiline and delamanid in line with the new WHO recommendations of August 2018 are significantly more expensive than the regimens recommended by WHO since 2016, with a price increase ranging from around 50% for regimens with only bedaquiline dispensed as a newer drug for 10 to 18 months, to more than 500% for regimens containing 20 months of both bedaquiline and delamanid. These price ranges take the TB community back to the level of unaffordability of DR-TB care in the early 2010s.

© Daro Sulakauri

Goderdzi Rajabishvili visits the TB hospital in Tbilisi, Georgia, for his twice-daily infusion of imipenem, an antibiotic used to treat MDR-TB. Each infusion takes an hour.

In July 2018, J&J reduced the price of six months of bedaquiline to US$400 (US$67/month) for all countries procuring through GDF.[38] At this price, the target regimen price of US$500 remains out of reach for many, especially for people with resistance patterns that are difficult to treat and who may need bedaquiline[39] or delamanid for more than the standard six months.

The South African Ministry of Health adapted its DR-TB guidelines in June 2018[9] to substitute the injectable drug kanamycin, which costs only pennies a day, with bedaquiline as an adapted version of the standardised shorter MDR-TB regimen (WHO 2016). As a result, the price of the recommended regimen in South Africa increased to US$852 based on GDF estimations,[40] almost twice the price of the shortened regimen (US$488) recommended by WHO before August 2018.

Unless further price reductions are achieved for certain DR-TB medicines, such as bedaquiline, delamanid, clofazimine, linezolid and imipenem-cilastatin, their unaffordability will negatively impact swift scale-up of the new WHO-recommended all-oral regimens, as well as implementation of shorter new DR-TB regimens currently being assessed in ongoing clinical trials. In particular, the newer medicines are unaffordable for countries without financial donor support, in an international context where donor support is shrinking.

TABLE 1: DR-TB REGIMEN PRICING, 2012-2018

Regimens are tailored to the individual person's disease profile, hence many different drug combinations are currently in use and this will only increase with the implementation of WHO recommendations. Therefore, below are the estimated cost of some possible individual longer and shorter regimens using pre- and post-WHO 2018 recommendations. All regimen prices are calculated based on the lowest price available for each quality-assured medicine in the GDF catalogue (GDF pooled procurement price).[41,42]

	2012	2015	2018	% change in GDF price (2012-2018)
Longer Regimens – pre-WHO 2018 recommendations 24-month regimen for all drugs, except Km/Cm (8 months)				
Lfx-Km-Cs-Pto-Z	US$1,719	--	US$742	-100%
Mfx-Cm-Cs-Eto-Z	US$3,953	US$1,820	US$1,314	-200%
Longer Regimens – WHO 2018 recommendations Examples of possible regimens based on the new WHO recommendations				
Lfx-Bdq-Lzd-Cfz-Cs (18 months)			US$2,335	
Lfx-Bdq-Lzd-Cfz-Cs (6 months) / Lfx-Bdq-Cfz-Cs (14 months), if Lzd is not tolerated for >6 months			US$2,204	
Bdq-Lzd-Cfz-Dlm-Ipm/Cln-Amx/Clv (6 months) / Bdq-Lzd-Cfz-Dlm (14 months), for fluoroquinolone-resistant patients			US$8,883	
Shortened Regimens				
Standardised shorter MDR-TB regimen (WHO 2016) **Pre-WHO 2018 recommendations** Km-Mfx-Pto-Cfz-Z-H^h-E (4 months) and Mfx-Cfz-Z-E (5 months) **WHO 2018 recommendations** Am-Mfx-Pto-Cfz-Z-H^h-E (4 months) and Mfx-Cfz-Z-E (5 months)	US$751 --		US$488 US$572	-35%
WHO 2018 recommendations Bdq-Lfx-Lzd-Dlm-Z (9 months)* Bdq-Lfx-Pto-Cfz-Z-H^h-E (4 months) / Bdq-Lfx-Cfz-Z-E (6 months)* *to implement under operational research conditions			US$3,373 US$1,020	

Am=amikacin, Amx/Clv=amoxicillin/clavulanate, Bdq=bedaquiline, Cfz=clofazimine, Cm=capreomycin, Cs=cycloserine, Dlm=delamanid, E=ethambutol, Eto=ethiomanide, H^h=high-dose isoniazid, Ipm/Cln=imipenem/cilastatin, Km=kanamycin, Lfx=levofloxacin, Lzd= linezolid, Mfx=moxifloxacin, Pto=prothionamide, Z=pyrazinamide

TABLE 2: PRICING TRENDS FOR KEY DR-TB MEDICINES

Medicine	% change in GDF price (2015-2018)
Linezolid (600mg)	-451%
Moxifloxacin (400mg)	-110%
Prothionamide (250mg)	-59%
Levofloxacin (500mg)	-26%

DON'T MISS OUR ONLINE SUPPLEMENT

The Online Supplement to the 5th edition of "DR-TB Drugs Under the Microscope" includes additional information on drug prices and quality, registration status, and paediatric formulations available to treat children with DR-TB. Company contacts and conditions of offer are also presented.

⋅⋅⋅ msfaccess.org/utm5

BEDAQUILINE

J&J holds the patent for bedaquiline in many countries, including India until 2023. In response to pressure regarding the initial high price of bedaquiline for low- and middle-income countries (US$900 and US$3,000 for a six-month treatment course, respectively), J&J began a donation programme with USAID in April 2015 for Global Fund-eligible countries, which ends in March 2019. In July 2018, J&J announced a price of US$400 for a six-month treatment course for all countries procuring through the GDF, regardless of their gross national income and national TB prevalence.[38] In order to ensure sustainable prices and supply through additional manufacturers, MSF sent an open letter to J&J in September 2018[43] urging J&J to issue non-exclusive voluntary licenses for bedaquiline to the Medicines Patent Pool for all low- and middle-income countries and all high TB burden countries. The letter also urged J&J to further reduce prices to a maximum of US$192 for six months (US$32 per month), which is important for all patients, including those who will need to take bedaquiline for longer than six months.

J&J entered into a partnership with Pharmstandard[44] for the manufacturing, registration and supply of bedaquiline in the Commonwealth of Independent States (CIS) and Georgia. Since both companies retain mutually exclusive market footprints, this is not expected to create any competition in price. In fact, Pharmstandard is charging US$1,584 for a six-month treatment with its bedaquiline tablets in the Russian Federation, which is almost four times higher compared to the new J&J price at GDF. This higher price will apply to all CIS countries and Georgia when the USAID/J&J donation programme ends, and to countries no longer eligible for Global Fund funding. This will be especially problematic for low-income countries in the region such as Kyrgyzstan and Tajikistan (see Table 3, "High prices of key adult formulations of DR-TB medicines", page 10), but also for other highly endemic countries. MSF also urges Pharmstandard to lower the price to US$32 per month.

DELAMANID

Delamanid is patented in many countries, including India until 2023, making Otsuka, the originator company, the sole supplier. The price of a six-month treatment course of delamanid remains very high, at US$1,700 for countries procuring through the GDF. Otsuka has partnerships with R-Pharm[45] for CIS and Georgia, and with Mylan for supply and registration in Afghanistan, Bangladesh, Brazil, Cambodia, Democratic Republic of Congo, Ethiopia, India, Kenya, Mozambique, Nigeria, Pakistan, South Africa, Tanzania, Uganda and Zimbabwe, as well as all other countries where Otsuka has no commercial presence.

These partnerships are not expected to lead to any competition in price, since again, the three companies retain mutually exclusive market footprints. MSF calls on Otsuka to considerably lower the price for delamanid, and to issue non-exclusive voluntary licenses to the Medicines Patent Pool for all low- and middle-income countries and high TB burden countries in order to ensure long-term sustainable supply to TB programmes. MSF also calls on the pharmaceutical corporation to be transparent about the terms and conditions of its agreement with Mylan to ensure that it meets the needs of DR-TB patients and TB programmes.

LINEZOLID

Despite the significant decrease in the price of linezolid since the entry of new generics manufacturers, this critical drug remains far too expensive for most governments to afford at a minimum of US$175 for six-month treatment. The estimated generic price target indicates that the current lowest available price could be further reduced by 50-80%.[46] Considering that linezolid is a core DR-TB drug – meaning all DR-TB patients should receive linezolid – as part of the new WHO recommendations, it is urgent to reduce the price to enable countries to ensure the best treatment for their patients. The increased global demand split across the current seven suppliers of quality-assured manufacturers worldwide should allow shortages to be avoided. The larger volumes soon to be procured worldwide should allow producers to decrease further their price per unit.

CLOFAZIMINE

Due to little interest in manufacturing this off-patent medicine, clofazimine has been under monopoly control by just one quality-assured supplier (Novartis). In August 2018, Macleods was granted ERP status for two new tablet formulations (50 and 100mg), which should result in the first quality-assured generic version becoming available in 2019.

The development of tablet formulations is an improvement for countries with hot and humid climates, where the soft capsules supplied by Novartis are challenging to store and transport. A second generics manufacturer in South Korea is also working on clofazimine. In the meantime, the addition of even one supplier will help meet any growth in demand for clofazimine linked to the implementation of the new WHO recommendations in which clofazimine becomes a Group B core drug; however, it is expected that the current high price of clofazimine (US$59 per month) will remain a major barrier to broader implementation of this regimen.

IMIPENEM-CILASTATIN

Imipenem-cilastatin is often an essential drug as part of a regimen with the newer DR-TB medicines bedaquiline and delamanid for people with pre-XDR and XDR-TB. Although several generics manufacturers produce imipenem-cilastatin, it remains a niche medicine because of its limited use for both TB and other infectious diseases. Low volumes are one reason that the price hasn't come down and remains as unaffordable as US$425 per month, even for the lowest GDF price and without taking into account the cost of the Port-a-Cath device[47] needed to administer the twice-daily injections of imipenem-cilastatin.

TABLE 3: HIGH PRICES OF KEY ADULT FORMULATIONS OF DR-TB MEDICINES

Medicine	Current price per patient per month	Target price for generic versions
Bedaquiline (50mg) Prices listed here apply to countries ineligible for the USAID/J&J donation programme	Countries purchasing through GDF + South Africa[48]: Janssen (J&J) US$67 Commonwealth of Independent States and Georgia: Pharmstandard US$264	US$8-17
Clofazimine (100mg)	Novartis US$59	US$4-11
Delamanid (50mg)	Otsuka US$283	US$5-16
Imipenem-cilastatin (500mg-500mg)	Lowest GDF price (multi-generic source drug) US$425	
Linezolid (600mg)	Lowest GDF price (multi-generic source drug) US$29	US$5-13

Notes:

• Target price ranges are based on the estimated costs of active and inactive pharmaceutical ingredients, formulation and packaging, and calculated according to a cost-plus model, which includes a reasonable profit margin. Prices could reach these levels with adequate market competition and transparency.[46]

• Since April 2015, bedaquiline has been made available free to Global Fund-eligible countries through a donation from USAID and J&J, but this donation programme will end in March 2019.

• The price of a treatment per patient per month with imipenem-cilastatin does not include the cost of the necessary Port-a-Cath[47] to be inserted under the skin of the chest for the twice-daily injections.

THREAT #2: DONOR FUNDING RETREAT

For the last 16 years, the Global Fund has made significant strides in helping countries access quality-assured medicines at more favourable prices. And over the past 10 years, GDF has helped improve access to more affordable quality TB medicines by using pooled procurement and competitive tenders to reduce prices, increasing the use of quality-assured medicines, improving pricing transparency, and attracting more manufacturers.

Since 2009, GDF's efforts have been strengthened through collaboration with the Global Fund to coordinate on pooled procurement, demand forecasting, market shaping, and other activities. Countries receiving Global Fund financing for TB are required to purchase DR-TB medicines through the GDF, enabling them to access the lowest prices for quality-assured medicines.

Some of the more dramatic price reductions achieved over the past three years (see Table 2, "Pricing trends for key DR-TB medicines", page 8) are due to GDF's improved procurement strategies implemented for their tendering processes every two years in the wake of the agreement with Global Fund. Pooled procurement across 139 countries in GDF's June 2018 competitive tender is expected to enable savings of an estimated US$31 million by March 2019.[49]

Additionally, manufacturers with good manufacturing practices have benefitted from being listed as a supplier of quality-assured medicines to GDF, as the GDF only procures medicines that have been approved through the WHO Prequalification Programme, the GDF ERP,[50] or a Stringent Drug Regulatory Authority (SDRA).

This has helped attract new manufacturers to the TB medicines market, thus securing a more sustainable supply.

Worryingly, this positive dynamic is threatened by stagnating donor funding for the Global Fund, accelerated withdrawal of Global Fund support from some national TB programmes, and overly ambitious co-financing, whereby countries are expected to purchase greater proportions of TB medicines using national funding. As countries transfer the procurement of TB medicines from the GDF to national procurement processes, the market for DR-TB medicines could re-fragment, threatening the gains seen over the past decade in price reductions and a growing catalogue of quality-assured TB medicines, with a likely negative impact on patients' access to TB treatment.

As countries face the challenges of implementing the new WHO DR-TB treatment recommendations and managing rising expenses linked to the use of bedaquiline as a core drug for the majority of DR-TB patients, obtaining DR-TB medicines through GDF at the best global benchmark prices will be even more crucial. Support to countries from GDF on forecasting drug supplies for newer regimens and optimising stock management will also be critically important. In addition, the Global Fund should allow countries to repurpose funding to facilitate the discontinuation of injectable aminoglycosides (kanamycin and capreomycin) and the introduction of bedaquiline, in combination with linezolid and fluoroquinolones, to facilitate rapid adoption of the new WHO DR-TB treatment recommendations.

THREAT #3: NATIONAL PROCUREMENT RISKS AND WEAKNESSES

For countries striving to access more affordable medicines, weak national tendering processes can be a barrier to accessing affordable and quality-assured medicines. Without strong national procurement mechanisms in place, countries that have relied on GDF procurement could have less flexibility to procure affordable, quality-assured TB medicines, and they could lose out on rapid introduction of new medicines and other tools needed to promote better treatment outcomes, including shorter and safer DR-TB regimens.

Adequate technical and financial support from the Global Fund and other donors for countries transitioning to co-financing or self-financing could help ensure that countries can procure quality-assured medicines at affordable prices through their national government tenders. Without this support and the time necessary to make reforms to national procurement frameworks, countries risk the known pitfalls of national tendering and fragmented procurement that can lead to high prices and the use of suboptimal medicines, which is particularly important as countries transition to more optimal DR-TB regimens and increase their use of bedaquiline.

One obstacle to national procurement can be the inability to attract any bidders, for example in comparatively small markets that are not prioritised by suppliers. This is especially common in the area of paediatric formulations, but has occurred even with first-line TB drugs for adults. In these cases, needed medicines may simply not be available in the country at all. Even when countries are successful in attracting bidders, those purchasing smaller volumes of medicines end up paying significantly higher prices because they do not have the ability to negotiate volume-based discounts or to drive competition across suppliers.

Furthermore, some drug tenders don't include requirements that meet WHO quality standards, and this may result in products of substandard or unknown quality being dispensed. Some drug tenders are disease-specific, which precludes consideration of repurposing those medicines for other indications, including TB, when considering overall volume and price.

National legislation often prioritises the use of locally produced or procured medicines, and in cases where local products are not available from quality-assured sources or in optimal formulations, such as fixed-dose combinations, people with DR-TB may lose out on accessing the medicines they need for effective treatment.

All countries should ensure that their national procurement frameworks allow the use of international procurement mechanisms, such as GDF for TB health products, to access quality-assured products at the lowest available prices, in order to make informed decisions about whether to use competitive national tenders or benefit from pooled procurement across countries. It's critical that the Global Fund and other donors support strong procurement systems in countries that face reduced donor funding and risk losing the associated benefits of an international pooled procurement mechanism.

© Sophie McNamara

Elizabeth (last name withheld), right, is visited by an MSF community health worker at her home in Port Moresby, Papua New Guinea. Elizabeth is being treated for drug-resistant TB.

THREAT #4: SPOTTY NATIONAL REGISTRATION OF KEY DR-TB DRUGS

Another significant barrier to implementing the new WHO recommendations is that key DR-TB medicines aren't registered for use in all countries that need them. When a medicine is not registered in a given country, importation of the medicine may be blocked, and manufacturers may be deterred from participating in government tenders. In addition, national TB programmes may be reluctant to include unregistered medicines in their treatment guidelines, even when their use is recommended by WHO.

None of the five key DR-TB medicines – bedaquiline, delamanid, linezolid, clofazimine and imipenem-cilastatin – are registered for TB use in all high TB burden countries (see Online Supplement available at msfaccess.org/utm5).

Encouragingly, Novartis has submitted an updated registration file with DR-TB clinical data for clofazimine to be registered as a TB medicine in South Africa. If local marketing authorisation is granted by the South African regulatory authorities, it would be the first time that clofazimine would be registered for TB in a country with a high TB burden. Unfortunately, in the case of linezolid, Pfizer, the innovator company, has so far shown no willingness to invest in a similar approach.

In some countries, pharmaceutical companies have no legal representation or local partner licensed to file the registration and bear the legal responsibility for the duration of the marketing authorisation. This can preclude registration of the drug. Pakistan is facing this issue with J&J, and as a result, sustainable access to bedaquiline is at risk there.

Countries and manufacturers can take steps to accelerate registration of key DR-TB medicines, including making use of existing mechanisms designed for this purpose, and to allow importation via waiver until local registration is complete. In the case of repurposed medicines – medicines originally approved to treat another disease but now also used to treat DR-TB – governments and manufacturers could, at a minimum, work to register these medicines for the original indication, as there may be more data available for the core indication that can facilitate the registration procedure and importations for DR-TB needs.

For example, clofazimine could be registered locally for leprosy as a first step in some contexts, while imipenem-cilastatin and linezolid can be registered for other infectious diseases, such as pneumonia for linezolid, and lower respiratory, intra-abdominal, and urinary tract infections for imipenem-cilastatin. Registration for other indications can ease importation procedures even when medicines are ordered for TB purposes. However, in some countries, the lack of a TB indication remains a barrier to access, particularly if those countries issue disease-specific tenders, as does South Africa.

Countries are encouraged to ensure that their laws recognise other reliable regulatory assessments and enable the use of available mechanisms designed to expedite registration procedures. The following mechanisms can enable swift regulatory evaluation with minimal investment:

EXPEDITED REGISTRATIONS OF SDRA-REGISTERED AND WHO-PREQUALIFIED MEDICINES

Ukraine has a provision allowing expedited registration of SDRA-registered medicines in less than 30 days.[51] J&J made use of this provision for bedaquiline and was granted marketing authorisation in June 2018. Otsuka has applied for expedited registration for delamanid and is awaiting a final decision from the Ukrainian National Drug Regulatory Authority (NDRA). Kyrgyzstan also has a provision covering expedited registration of both SDRA-registered and WHO-prequalified medicines.[52]

Additional countries, including Uzbekistan[53] and Moldova, are in the process of setting up similar regulatory flexibilities to allow the purchase and importation of quality-assured medicines for TB and other diseases. All countries should add such provisions to their national drug laws.

WHO COLLABORATIVE REGISTRATION PROCEDURE

The WHO Collaborative Registration Procedure targets 90 days for local registration of WHO-prequalified and SDRA-registered products.[54] Manufacturers still need to submit a registration file at country level.

For WHO-prequalified medicines, the technical assessment of the product dossier by the WHO Prequalification team is shared with the local NDRA. In June 2018, 352 medicines (including 74 TB medicines) were registered locally through this mechanism by 14 generics manufacturers in 24 countries.

For SDRA-registered medicines, once an agreement is in place with the related SDRA (for example, the European Medicines Agency or US Food and Drug Administration), WHO plays an intermediary role between the SDRA and the local NDRA to facilitate the exchange of the SDRA's technical assessment. During the pilot phase in 2017, five medicines (including bedaquiline) were registered through this mechanism by three innovator companies in 17 countries. This SDRA-registered medicine procedure became a standard mechanism in May 2018.

SWISSMEDIC MARKETING AUTHORISATION FOR GLOBAL HEALTH PRODUCTS

In 2017, Swissmedic, Switzerland's agency for therapeutic products, initiated the Marketing Authorisation for Global Health Products,[55] a new initiative available to East African and other sub-Saharan countries to reduce the burden of regulatory assessment at country level and help accelerate access to medicines. Through this initiative, Swissmedic assesses product dossiers for medicines of global public health concern and invites other countries to directly join the technical evaluation or be observers in the process.

RESEARCH AND DEVELOPMENT:
Building a healthy pipeline for future TB treatments

While rapid scale-up of diagnosis and treatment of people with TB using currently available tools is imperative, we clearly need faster, safer and simpler tools in order to effectively achieve the WHO End TB goals. An estimated US$2 billion is needed annually[56] for innovation in TB research and development (R&D) for new tools and technologies to prevent, diagnose and treat TB, based on what's needed to ensure the fulfillment of the WHO End TB roadmap.[57]

A priority should be to accelerate research into new TB treatments that are effective, affordable and much easier for people to complete. Sustaining a healthy drug pipeline is necessary to deliver improvements to existing and future treatments, making them safer and shorter for treating drug-sensitive and drug-resistant TB. In parallel, development of more accurate, point-of-care (or near point-of-care) diagnostic and drug-sensitivity testing (DST) tools are needed to enable clinicians to compose the optimal treatment regimen for each person.

Today, the prevailing model of medical R&D has failed to deliver the health tools needed to effectively control TB. Effective TB treatment requires multiple drugs to be used together in a combination treatment regimen, but the way drugs are developed today results in new medicines being developed on a proprietary basis in isolation from drugs being developed by other companies or research entities. This separation causes missed opportunities and undue delays in the discovery of beneficial drug combinations and flagging of potentially negative drug-drug interactions early in the R&D process.

The drug companies have no incentives to test novel compounds together or to share clinical trial data, which would strengthen and accelerate regimen-based research. Instead, even though much of the research from discovery to the clinic is done by public research entities and/or is funded by public or philanthropic organisations, companies motivated to get approval for their new TB drugs as quickly as possible are usually the ones that will develop and market the drugs. This typically means adding the new drugs to existing regimens that may be long and toxic, and leaving new regimen development to the post-approval process, thereby wasting precious time and resources in getting better treatment options to patients.

This paradigm results in long delays in bringing new medicines into routine use in treatment programmes. On top of that, medicines are then often priced beyond the reach of many programmes and people in desperate need of better lifesaving TB treatment, based on profit motives. Companies continue to justify the need for high prices by claiming that large revenues are required to cover R&D costs. However, companies aren't required to be transparent about those drug-development costs. Too little public information is available on the levels of government and philanthropic funding that helped pay for the development of a particular medicine in the first place or show its clinical benefit in regimens. An example of this situation is the development of bedaquiline by J&J, which benefited from significant public funding and support, yet bedaquiline's price does not reflect this public investment. MSF sent an open letter to J&J in September 2018 urging the company to increase access to bedaquiline.[43]

R&D efforts for TB must evolve to focus on drug *regimen* development. A more open and collaborative R&D approach is needed to address the needs of patients and treatment providers: new regimens that are radically shorter, more effective, better tolerated, easy to take, and affordable (see Box below: "New DR-TB treatment regimens: what we need").

In addition, considering the fact that TB R&D is primarily financed through public and philanthropic funding, it is critical that public return on such investments in TB R&D is ensured by making the end results available and affordable to all who need them. In line with recent United Nations declarations and recommendations, funding should go towards research programmes that are needs-driven, evidence-based, and guided by the principles of affordability, effectiveness, efficiency, equity and 'de-linkage'.[58,59]

MSF has worked with civil society, patient groups, researchers and others to develop a checklist to help reduce the amount of time it takes for new drugs to be developed, tested and commercialised, keeping the needs of patients and treatment providers front and centre (see Box: "Reducing the time to patient for promising new drugs and regimens", page 14).

NEW DR-TB TREATMENT REGIMENS: WHAT WE NEED

- **All oral treatment** (*no injectables*)

- **Shorter duration** (*six to nine months*)

- **Effective for all forms of DR-TB** (*including RR-, MDR-, XDR-, pulmonary and extra-pulmonary TB*)

- **Effective formulations for children as well as adults**

- **Cocktail of novel classes of drugs** (*each from a distinct class of drugs, including at least 2-3 from a new drug class*)

- **Less toxic, with limited side effects** (*requiring minimal routine safety monitoring*)

- **Minimal drug-drug interactions** (*particularly with antiretroviral therapy*)

- **Easy to transport, store and administer** (*no cold chain, long half-life, simple dosing schedule*)

- **Conducive to good antimicrobial stewardship to prevent drug resistance**

- **Affordable** (*less than $500 per treatment course*)

Sources: see references 60, 61, 62

CHECKLIST: REDUCING THE TIME TO PATIENT FOR PROMISING NEW DRUGS AND REGIMENS

The following should be considered as a pro-access pathway to reduce the 'time to patient' and barriers to access, in order to reach people in need with more effective and safer DR-TB treatment as drugs and regimens emerge from the development pipeline.

Target product profile (TPP)	TPP is based on health needs with an affordability target built in. The specifications should include formulations for adults and children, and transport, storage and administration considerations, as well as provision for comprehensive drug-drug interaction studies
Trial data	Trial data are shared, available upon request, or available on a common information platform
Access to compounds	Researchers have free access to compounds for testing regimens and carrying out drug-drug interaction studies
Regulatory approval	Drug approval application is submitted for emerging drugs and regimens
Licensing	Proprietary owners issue non-exclusive voluntary licensing for all low- and middle-income countries and those with high TB burdens
Early access/compassionate use	Provision for early access and compassionate use is established with non-onerous pharmacovigilance requirements
WHO approval and normative guidance	• WHO guideline committee is convened and WHO issues guidance in a timely manner • Drug is added to Essential Medicines List • Drug is added to Prequalification Expression of Interest • Drug dossiers are submitted to WHO Prequalification Programme • Procurement entity (GDF) issues request for ERP review of the product (ERP approval enables procurement pending full WHO prequalification) • WHO retrains Global Laboratory Initiative[63] and Green Light Committee[64] • New guidance/guidelines are disseminated through regional and country WHO mechanisms
Market dynamics and entry	Unitaid and other global health actors support an agency to carry out market forecasting, analysis and entry, including encouraging generics manufacturers to ensure sustainable supply and affordable prices
National regulatory frameworks	• Manufacturers submit drug for the WHO Collaborative Registration Procedure • Manufacturers submit dossiers to National Drug Regulatory Agencies (NDRAs), prioritising high-burden countries, and make public the registration plan and status • NDRAs consult TB clinicians and TB programme on the medical need for the drug/regimen at the time when the dossier is filed • Countries fast-track registration of novel classes of TB drugs
Funding rollout	• WHO develops a 'transition' plan to phase out older/less optimal therapies and implement new guidance with role for Global Fund and donors • Countries include implementation of new guidance in concept notes and revise/renegotiate grants accordingly • The Global Fund TB Situation Room tracks/acts on progress/delays

CONCLUSION:
Recommendations to frame a better future

Mounting an effective response to the TB global health emergency requires stronger political commitments by world leaders to prevent, diagnose and treat TB through patient-centred care, and to accelerate research into new TB medicines, diagnostic tools and vaccines that are effective, affordable and suitable to control TB. Much more needs to be done to reduce death and illness from TB, including from its drug-resistant forms.

Governments and the TB community should seize the opportunity to improve DR-TB outcomes through supporting responsible and rapid implementation of the new WHO DR-TB treatment recommendations.

Governments, donors, drug companies and global health organisations must work to overcome challenges in access to effective TB treatment by implementing the following recommendations:

MANUFACTURERS AND DRUG DEVELOPERS

- Make use of expedited registration procedures wherever possible (for example, the WHO Collaborative Registration Procedure) and prioritise countries with high TB burdens

- Provide sustainable medicine prices to support affordable DR-TB regimens and refrain from using patents to block alternative suppliers or extend monopolies

- Set up clinical development strategies that generate evidence required to optimise clinical practice and case management, especially for underserved populations in resource-limited settings

- Develop early-access and compassionate-use programmes for new medicines based on positive efficacy and safety treatment outcomes

- Provide transparent access to R&D costs for new DR-TB health products and data generated by research programmes

- Share raw data from trials for WHO guidelines review

COUNTRIES

- Update national TB treatment guidelines and national essential medicines lists according to the latest WHO recommendations including the new DR-TB recommendations announced in August 2018

- Join the WHO Collaborative Registration Procedure for WHO-prequalified and SDRA-registered products

- Use import waivers until local registration is available and efficient registration procedures are in place

- Ensure national procurement rules allow for pooled procurement, including through international mechanisms such as GDF

- Consider requiring WHO prequalification or SDRA approval for TB medicines and encourage national manufacturers to submit to the WHO Prequalification Programme

- Ensure access and quality of phenotypic drug-resistance testing for all relevant drugs, including new drugs, as recommended by WHO

- Utilise TRIPS flexibilities and other safeguards to ensure sustainable supply by encouraging alternative suppliers, which increases competition and lowers prices

- Mobilise and fund the research community to engage in TB R&D, including collaborative platforms, commitments to share data and molecules and to make the end products affordable and accessible, including by ensuring de-linkage of the cost of R&D from the product price

WHO

- Provide advice and technical support to countries on implementation of the new RR-TB and MDR-TB treatment guidelines to be published in November 2018, in particular to:

  - Translate the new medicines groupings into practical guidance for regimen construction

  - Aid in the transition to regimens free of injectable aminoglycosides (kanamycin and capreomycin)

  - Manage financial and logistical constraints on drug supply, local programmatic considerations, and competing priorities during implementation of the new recommendations

- Ensure all Supranational Reference Laboratories (SRLs) have capacity for drug sensitivity testing (DST) of new drugs and sequencing to support external testing for all countries

DONORS

- The Global Fund should provide technical assistance to countries slated for transition and co-financing to ensure that their national procurement and regulatory systems can continue to secure access to affordable, quality-assured and WHO-recommended formulations of TB medicines

- The Global Fund should allow countries to repurpose funding for the injectables kanamycin and capreomycin to other core medicines to facilitate rapid adoption of the new WHO DR-TB treatment guidelines

- The Global Fund and Unitaid should allocate funds to countries to compensate financial loss due to kanamycin and capreomycin disposal

- Support civil society in playing a watchdog role to ensure transparency of national procurement of affordable, quality-assured and WHO-recommended formulations of TB medicines

- Support WHO Prequalification Programme

- Support and significantly increase funding for TB R&D, including collaborative research platforms such as the Life Prize and other initiatives that aim to develop regimens, and commit to share data and molecules, and make the end products affordable and accessible

ANNEX 1: SUMMARY TABLE OF PRICES PROVIDED BY PHARMACEUTICAL COMPANIES

The price corresponds to the price of one unit (tablet, capsule, etc)

Percentages indicate price evolution (in USD) of the lowest available GDF price* comparing 2015 to 2018

Drug	GDF indicated prices (2015)	GDF indicated prices (06.2018)	All known SDRA-approved and/or WHO-prequalified and/or Expert Review Panel temporary approved sources**							
Amikacin			Bros	Cipla	Medochemie	Pharmatex	Vianex	Pharmathen Hellas	Qilu Pharmaceuticals	
500mg/2ml solution for injection	0.678 - 0.805	0.690 - 0.705 +2%	X	X	X	X	X	X	X	
Kanamycin			Macleods	Meiji	PanMedica/ Panpharma	Hisun				
0.5g powder for injection	--	0.850	X	--	--	X				
1g powder for injection	1.000 - 1.721	0.680 - 0.920 -47%	X	--	X	X				
1g/4ml solution for injection	2.560	2.366 -10%	--	X	--	--				
Capreomycin			Akorn	King Pharmaceuticals	Hisun	Macleods	Mylan	NCPC	Vianex	
0.5g powder for injection	--	3.750	--	--	--	X	--	--	--	
1g powder for injection	3.800 - 4.700	2.170 - 3.850 -75%	X	X	X	X	X	X	X	
Moxifloxacin			Cipla	Hetero	Macleods	Microlabs	Sunpharma	Bayer	Mylan	MSN Laboratories
400mg tablet	0.437 - 0.540	0.208 - 0.910 -110%	X	X	X	X	X	X	X	X
Levofloxacin			Apotex	Cipla	Hetero	Macleods	Microlabs	Denk Pharma	Medochemie	HEC
250mg tablet	0.033 - 0.055	0.027 - 0.038 -22%	X	X	X	X	X	X	X	X
500mg tablet	0.059 - 0.097	0.047 - 0.063 -26%	X	X	X	X	X	X	X	X
750mg tablet	0.100	0.102 - 0.205 +2%	X	--	X	X	--	--	--	--
Ethionamide			Macleods	Cipla	Lupin	Microlabs				
125mg tablet	--	0.081	X	--	--	X				
250mg tablet	0.062 - 0.080	0.079 - 0.097 +22%	X	X	X	X				
Prothionamide			SW Pharma GmbH	Lupin	Microlabs	Olainfarm				
250mg tablet	0.130 - 0.178	0.082 - 0.155 -59%	X	X	X	X				

* http://www.stoptb.org/gdf/drugsupply/drugs_available.asp (click on Ordering List of TB Medicines)
** https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/

Drug	GDF indicated prices (2015)	GDF indicated prices (06.2018)	All known SDRA-approved and/or WHO-prequalified and/or Expert Review Panel temporary approved sources							
Cycloserine			Cipla	Dong-A	Macleods	Strides	Biocom JSC	Chaos Centre	Mylan	
250mg capsule	0.187 - 0.330	0.193 - 0.268 +3%	X	X	X	X	X	X	X	
Terizidone			SW Pharma GmbH	Macleods						
250mg capsule	1.588 - 1.666	1.666 - 1.800 +5%	X	X						
PAS			Jacobus							
4g sachet	1.333	1.333	X	--						
PAS-sodium			Macleods	Olainfarm						
60% w/w granules – 9.2g sachet	1.690	1.240 -36%	X	--						
Powder for oral solution – 5.52g sachet	1.370	1.320	--	X						
Clofazimine			Novartis							
50mg soft-gel capsule	0.547 - 0.713	Not available at GDF	X							
100mg soft-gel capsule	1.095 - 1.267	0.982 -11%	X							
Linezolid			Hetero	Macleods	Pfizer	Teva	Dr Reddy's	Fresenius Kabi	Cipla	Sandoz
600mg tablet	5.350 - 5.480	0.970 - 1.400 -451%	X	X	X	X	X	X	X	X
Imipenem / cilastatin			Demo	Sunpharma	PanMedica / Panpharma	Fresenius Kabi	Labatec			
500mg/500mg, powder for injection	--	3.100 - 3.600	X	X	X	X	X			
Meropenem			Demo	PanMedica/ Panpharma	Vianex					
1g powder for injection	--	3.700	X	X	X					
Bedaquiline			Johnson & Johnson							
100mg tablet	0.00 Donation	0.00 Donation	X							
Delamanid			Otsuka							
50mg film-coated tab	2.530	2.530	X							

REFERENCES

1 WHO. Global tuberculosis report 2018. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.who.int/tb/publications/global_report/en/

2 WHO. The top 10 causes of death. [Online]. 2018 May 24 [Cited 2018 Sep 24]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/

3 Médecins Sans Frontières. International Activity Report 2017. 2017 in figures. [Online]. 2017 [Cited 2018 Sep 24]. Available from: https://www.msf.org/international-activity-report-2017/2017-figures

4 EndTB clinical trial. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.endtb.org/clinical-trial

5 Médecins Sans Frontières. TB PRACTECAL: A pragmatic clinical trial for effective, concise and less-toxic treatment regimens. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://www.msf.org.uk/tb-practecal

6 WHO. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). [Online]. 2018 August [Cited 2018 Sep 24]. Available from: http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf

7 WHO. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. [Online]. 2016 Oct [Cited 2018 Sep 24]. Available from: http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/

8 EndTB interim analysis. Bedaquiline- and delamanid-containing regimens achieve excellent interim treatment response without safety concerns. [Online]. 2018 Jul 13 [Cited 2018 Sep 24]. Available from: http://www.endtb.org/resources/endtb-interim-analysis-july2018

9 Republic of South Africa, Department of Health. New Bedaquiline data shows reduction in TB mortality cases. Media statement. [Online]. 2018 Jun 18 [Cited 2018 Sep 24]. Available from: http://www.tbonline.info/media/uploads/documents/new_bedaquiline_data_shows_reduction_in_tb_mortality_cases.pdf

10 Schnippel K, Ndjeka N, Maarten G, Meintjes G, Master I, Ismail N, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018;6(9):699-706. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1016/S2213-2600(18)30235-2

11 Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. Eur Respir J 2017;e50(1):1700311. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1183/13993003.00311-2017

12 Mok J, Kang H, Hwang SH, Park JS, Kang B, Lee T, et al. Interim outcomes of delamanid for the treatment of MDR- and XDR-TB in South Korea. J Antimicrob Chemother 2018;73(2):503-508. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1093/jac/dkx373

13 Hewison C, Ferlazzo G, Avaliani Z, Hayrapetyan A, Jonckheere S, Khaidarkhanova Z, et al. Six-month response to delamanid treatment in MDR TB patients. Emerg Infect Dis 2017;23(10):1746-1748. [Cited 2018 Sep 24]. Available from: https://doi.org/10.3201/eid2310.170468

14 Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003;289(16):2120-2127. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1001/jama.289.16.2120

15 Ferlazzo G, Mohr E, Laxmeshwar C, Hewison C, Hughes J, Jonckheere S, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. Lancet Infect Dis 2018;18(5):536-544. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1016/S1473-3099(18)30100-2

16 Seung KJ. Accelerating TB elimination through access to bedaquiline and delamanid [oral presentation]. 2017 Oct 12. [Cited 2018 Sep 24]. Available from: http://theunion2017.abstractmgmt.com/files2017/610_10_4_1400_Seung.pptx

17 Guglielmetti L, Jaspard M, Le Dû D, Lachâtre M, Marigot-Outtandy D, Bernard C, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J 2017;49(3):1601799. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1183/13993003.01799-2016

18 TB Alliance. Nix-TB. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://www.tballiance.org/portfolio/trial/5089

19 TB Alliance. ZeNix. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://www.tballiance.org/portfolio/trial/11883

20 Working Group on New TB Drugs. A phase 3 study assessing the safety and efficacy of bedaquiline plus PA-824 plus linezolid in subjects with drug resistant pulmonary tuberculosis. [Online]. 2015 Feb [Cited 2018 Sep 24]. Available from: https://www.newtbdrugs.org/pipeline/trials/nix-tb-b-pa-l

21 Conradie F, Diacon AH, Everitt D, Mendel C, van Niekerk C, Howell P, et al. The Nix-TB trial of pretomanid, bedaquiline and linezolid to treat XDR-TB. Abstract 80LB. Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, Washington. [Online]. 2017 Feb 13-16 [Cited 2018 Sep 24]. Available from: https://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb

22 TB Alliance. SimpliciTB. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://www.tballiance.org/portfolio/trial/11937

23 ClinicalTrials.gov. [Online]. Bethesda (MD): National Library of Medicine (US). Trial to evaluate the efficacy, safety and tolerability of BPaMZ in drug-sensitive (DS-TB) adult patients and drug-resistant (DR-TB) adult patients. Identifier: NCT03338621. 2017 Nov [Cited 2018 Sep 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT03338621

24 ClinicalTrials.gov. [Online]. Bethesda (MD): National Library of Medicine (US). Evaluating newly approved drugs for multidrug-resistant TB (endTB). Identifier: NCT02754765. 2018 Apr [Cited 2018 Sep 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT02754765

25 ClinicalTrials.gov. [Online]. Bethesda (MD): National Library of Medicine (US). An open-label RCT to evaluate a new treatment regimen for patients with multi-drug resistant tuberculosis (NEXT). Identifier: NCT02454205. 2016 Oct 26 [Cited 2018 Sep 24]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02454205

26 ClinicalTrials.gov. [Online]. Bethesda (MD): National Library of Medicine (US). Pragmatic clinical trial for a more effective concise and less toxic MDR-TB treatment regimen(s) (TB-PRACTECAL). Identifier: NCT02589782. 2018 Mar 15 [Cited 2018 Sep 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT02589782

27 International Union Against Tuberculosis and Lung Disease. Clinical Trials. Current Trials: STREAM Stage 2. [Online]. 2016 Apr [Cited 2018 Sep 24]. Available from: https://www.theunion.org/what-we-do/research/clinical-trials

28 ClinicalTrials.gov. [Online]. Bethesda (MD): National Library of Medicine (US). The evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB (STREAM). Identifier: NCT02409290. 2018 Jan 26 [Cited 2018 Sep 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT02409290

29 treatTB. Technology, Research, Education, and Technical Assistance for Tuberculosis. STREAM Trial. Available from: http://www.treattb.org/overview/

30 ClinicalTrials.gov. [Online]. Bethesda (MD): National Library of Medicine (US). Safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary TB, XDR-TB, pre-XDR-TB or non-responsive/intolerant MDR-TB (ZeNix). Identifier: NCT03086486. 2018 Feb 8 [Cited 2018 Sep 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT03086486

31 Sentinel Project on pediatric drug-resistant tuberculosis. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://sentinel-project.org/

32 WHO. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents. Interim policy guidance. [Online]. 2016 [Cited 2018 Sep 24]. Available from: http://apps.who.int/iris/bitstream/handle/10665/250614/9789241549899-eng.pdf

33 WHO. Model List of Essential Medicines for Children. 6th List. March 2017, amended August 2017. [Online]. 2017 Aug [Cited 2018 Sep 24]. Available from: http://apps.who.int/iris/bitstream/handle/10665/273825/EMLc-6-eng.pdf

34 Memorandum of Understanding between the Medicine Patent Pool Foundation and Otsuka Novel Products GmbH. [Online]. 2017 Oct 9 [Cited 2018 Sep 24]. Available from: https://medicinespatentpool.org/uploads/2017/10/MoU-Otsuka.pdf

35 Svensson EM, du Bois J, Kitshoff R, de Jager VR, Wiesner L, Norman J, et al. Relative bioavailability of bedaquiline tablets suspended in water: implications for dosing in children. Br J Clin Pharmacol 2018;84(10):2384-2392. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1111/bcp.13696

36 Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet 2014;383(9928):1572-1579. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1016/S0140-6736(14)60195-1

37 WHO. Roadmap towards ending TB in children and adolescents. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.who.int/tb/publications/2018/tb-childhoodroadmap/en/

38 Stop TB Partnership. South Africa ensures reduction of prices for Bedaquiline to benefit the world. [Online]. 2018 Jul 23 [Cited 2018 Sep 24]. Available from: http://www.stoptb.org/news/stories/2018/ns18_053.asp

39 Hewison C, Bastard M, Khachatryan N, Kotrikadze T, Hayrapetyan A, Avaliani Z, et al. Is 6 months of bedaquiline enough? Results from the compassionate use of bedaquiline in Armenia and Georgia. Int J Tuberc Lung Dis 2018;22(7):766-772. [Cited 2018 Sep 24]. Available from: https://doi.org/10.5588/ijtld.17.0840

40 Stop TB Partnership. WHO's Rapid Communication on treatment of multidrug- and rifampicin-resistant tuberculosis. Stop TB Partnership's statement on implications for TB programmes. [Online]. 2018 Aug 22 [Cited 2018 Sep 24]. Available from: http://www.stoptb.org/news/stories/2018/ns18_061.asp

41 Stop TB Partnershp. GDF Products List. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

42 Stop TB Partnership. Ordering List of TB Medicines. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.stoptb.org/gdf/drugsupply/pc4.asp

43 Médecins Sans Frontières. Open letter to J&J regarding affordable access to bedaquiline. [Online]. 2018 Sep 17 [Cited 2018 Sep 24]. Available from: https://msfaccess.org/sites/default/files/2018-09/TB_Letter_SecuringBedaquiline_JJ_2018_0.pdf

44 Pharmstandard company website. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://pharmstd.com/

45 R-Pharm company website. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://r-pharm.com/en/

46 Gotham D, Fortunak J, Pozniak A, Khoo S, Cooke G, Nytko FE, Hill A. Estimated generic prices for novel treatments for drug-resistant tuberculosis. J Antimicrob Chemother 2017;72(4):1243-1252. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1093/jac/dkw522

47 University Health Network (UHN), Toronto, Canada. What to Expect When Getting a Port-a-Cath. [Online]. 2014 Dec [Cited 2018 Sep 24]. Available from: https://www.uhn.ca/PatientsFamilies/Health_Information/Health_Topics/Documents/What_to_Expect_When_Getting_Port-a-Cath.pdf

❖ *References continued*

48 Low M. AIDS2018: Reduction in price of bedaquiline welcome, but is it enough? [Online]. 2018 Jul 24 [Cited 2018 Sep 24]. Available from: https://www.spotlightnsp.co.za/2018/07/24/aids2018-reduction-in-price-of-bedaquiline-welcome-but-is-it-enough/

49 Stop TB Partnership. USD 31 million saved by Stop TB Partnership's Global Drug Facility through newly-reduced prices for TB medicines. [Online]. 2018 Jun 14 [Cited 2018 Sep 24]. Available from: http://www.stoptb.org/news/stories/2018/ns18_043.asp

50 The Global Fund. Sourcing & Management of Health Products. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/

51 Legal Alliance [Ukraine]. The Ministry of Health will register the first drug under a simplified procedure. [Online]. 2017 Jul 24 [Cited 2018 Sep 24]. Available from: https://www.legalalliance.com.ua/eng/news/the-ministry-of-health-will-register-the-first-drug-under-a-simplified-procedure/

52 Kyrgyz Republic. Law on medical products circulation, #165 Law, 2017 August 2 [Russian]. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.pharm.kg/ru/legislation

53 Republic of Uzbekistan. About measures on increase of efficiency of the state registration of medical products and improvement of their provision of population [Russian]. [Online]. 2018 Jun 20 [Cited 2018 Sep 24]. Available from: https://www.norma.uz/raznoe/o_merah_po_povysheniyu_effektivnosti_gosudarstvennoy_registracii_lekarstvennyh_sredstv_i_uluchsheniyu_obespecheniya_imi_naseleniya

54 WHO. Collaborative Procedure for Accelerated Registration. Essential Medicines and Health Products: Prequalification of medicines. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://extranet.who.int/prequal/content/collaborative-procedure-accelerated-registration

55 Swissmedic. Factsheet: New partnership to accelerate access to quality health products. [Online]. 2018 [Cited 2018 Sep 24]. Available from: https://www.swissmedic.ch/dam/swissmedic/fr/dokumente/stab/networking/factsheet_new_partnershiptoaccelerateaccesstoqualityhealthproduc.pdf.download.pdf

56 Stop TB Partnership. Global plan to end TB: The paradigm shift 2016-2020. [Online]. 2015 [Cited 2018 Sep 24]. Available from: http://www.stoptb.org/global/plan/plan2/

57 WHO. WHO End TB Strategy. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.who.int/tb/post2015_strategy/en/

58 UN General Assembly. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance. [Online]. 2016 Sep 22 [Cited 2018 Sep 07]. Available from https://digitallibrary.un.org/record/842813/files/A_71_L-2-EN.pdf

59 The United Nations Secretary-General's High-Level Panel on Access to Medicines Report: Promoting Innovation and Access to Health Technologies. United Nations Secretary-General's High-Level Panel on Access to Medicines. [Online]. 2016 Sep 14 [Cited 2018 Sep 24]. Available from: http://www.unsgaccessmeds.org/final-report/

60 Brigden G, Nyang'wa B-T, du Cros P, Varaine F, Hughes J, Rich M, et al. Principles for designing future regimens for multidrug-resistant tuberculosis. Bull World Health Organ 2014;92:68-74. [Cited 2018 Sep 24]. Available from: http://www.who.int/bulletin/volumes/92/1/13-122028.pdf

61 Médecins Sans Frontières. DR-TB Drugs Under the Microscope: Sources and prices for drug-resistant tuberculosis medicines. 4th edition. [Online]. 2016 Mar 20 [Cited 2018 Sep 24]. Available from: https://msfaccess.org/dr-tb-drugs-under-microscope-4th-edition

62 Lienhardt C, Nahid P, Rich ML, Bansbach C, Kendall EA, Churchyard G, et al. Target regimen profiles for treatment of tuberculosis: a WHO document. Eur Respir J 2017;49(1):1602352. [Cited 2018 Sep 24]. Available from: https://doi.org/10.1183/13993003.02352-2016

63 Stop TB Partnership. Global Laboratory Initiative (GLI) website. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.stoptb.org/wg/gli/

64 WHO. The Green Light Committee (GLC) Initiative: Frequently Asked Questions. [Online]. 2018 [Cited 2018 Sep 24]. Available from: http://www.who.int/tb/challenges/mdr/greenlightcommittee/glc_faq.pdf

To access the report online: msfaccess.org/utm5   October 2018