ISSUE BRIEF

MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN

READY, SET, SLOW DOWN:

NEW AND PROMISING DR-TB DRUGS ARE GRABBING HEADLINES BUT NOT REACHING PATIENTS

MSF ON THE POLICIES UNDERPINNING THE DEADLY DR-TB TREATMENT GAP

THE GLOBAL DR-TB CRISIS

Drug-resistant tuberculosis (DR-TB) is a major global health emergency: An estimated 480,000 people have multi-drug resistant TB (MDR-TB), yet only 30% are diagnosed and treated. Resistant forms of TB, including extremely-drug resistant TB (XDR-TB), are increasingly spreading directly from person to person. The World Health Organization's (WHO) sobering *Global TB Report 2014* reports MDR-TB rates of 25-35% among newly diagnosed TB cases in Belarus, Kyrgystan and Kazakhstan. People lucky enough to receive medical care face two years of toxic treatment, including painful injections and thousands of pills, as a part of a regimen that is not only expensive (US$1,500-5,000 per treatment course) but delivers abysmal cure rates. Undiagnosed and untreated, the disease continues to spread and kill. The lack of good and affordable drugs, increasing levels of resistance, and the sheer number and breadth of DR-TB cases present a grave global challenge.

Finally, an opportunity exists to increase the chance for survival and cure. Bedaquiline, the first in a new class of TB drugs developed in 50 years, received accelerated approval for treating MDR-TB in 2012. A second new drug, delamanid, received approval in 2014. The TB drug pipeline has five new drugs in clinical testing. The WHO Prequalification Programme has approved nearly a dozen new producers of DR-TB medicines, and repurposed "group 5" medicines,* like clofazimine and linezolid, are showing effectiveness against TB.

However, phase one of the TB pipeline is sparse, with only one compound present, TBA 354; to date, fewer than 1,000 people worldwide have gained access to the new TB drugs; and we are still missing critical opportunities to test the new drugs together to deliver truly powerful and novel regimens. Clofazimine and linezolid are not yet registered for TB, which causes a significant barrier to their use.

New treatments provide new hope, yet no one drug can solve the crisis; what is urgently needed is an arsenal of regimens that are patient-friendly, quality-assured, safe, and efficacious, along with further developments in timely and accurate diagnosis.

TB FACTS IN 2014

- 9 million people affected by TB, and 1.5 million deaths
- 480,000 people with MDR-TB, yet only one in five treated
- 136,000 MDR-TB cases diagnosed
- In parts of Eastern Europe and Central Asia, MDR-TB rates in re-treatment cases are reaching 75%
- Cure rates for MDR-TB are 48% at best, dropping to 22% for XDR-TB

* The WHO group 5 drug classification refers to anti-TB drugs with unclear efficacy or an unclear role in MDR-TB treatment.

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ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

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NEW DRUGS PROVIDE NEW HOPE, BUT REMAIN LARGELY OUT OF REACH

Bedaquiline (Janssen) received fast-track approval by the US Food and Drug Administration (FDA) in December 2012, but the company has only submitted dossiers for registration


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in 21 countries outside the US and EU, and its pricing structure remains a barrier, especially when added to the existing costly regimen. Cost is particularly an issue for middle-income countries (MICs). A coalition of civil society and global health actors asked the company to revise its prices for low and middle-income countries – currently $900 and $3,000 respectively for a six-month course, with some high-burden MICs exceptionally receiving the LIC price – but to date the price structure remains unchanged. The unaffordability of Janssen's product is exemplified by the fact that two years after the drug was registered for use, Janssen and USAID announced a donation program to help some low- and middle-income countries finally access the drug without the price barrier. The exact details of the program are not yet known, but preliminary information indicates that it will be limited in geographic scope, timeframe and by the total quantity of treatment courses available. The donation programme in any case will not be able to fully meet the needs of DR-TB patients desperately in need of lifesaving treatment options.

Government funding contributed to research and development (R&D) for bedaquiline, and Janssen received a US FDA priority review voucher worth potentially 50% of its clinical trials costs. How these contributions are reflected in the end price, however, is not transparent. Some countries are also facing difficulties in meeting WHO's pharmacovigilance recommendations, which forms another costly barrier beyond the lack of country-level registration of the drug.

Delamanid (Otsuka) received approval from the European Medicines Agency (EMA) and Japan's Pharmaceuticals Medical Devices Agency (PMDA) in 2014, but the company has only submitted dossiers for registration in Europe, Japan and South Korea, and its pricing structure outside of these places is unknown. So far, delamanid is only marketed in the United Kingdom and in Germany. It is not clear whether the company intends to submit dossiers for registration in endemic countries or what their strategy will be regarding the negotiation of voluntary licenses.

Compassionate Use (CU):
MSF and some governments offer the new drugs to patients via compassionate use and similar programmes, in countries that have the necessary regulations in place. Early results from the use of a bedaquiline-containing treatment in MSF's treatment programme in Armenia show that the TB bacillus was undetectable in 54% (14/26) of patients at two months, and in 84% (22/26) of patients at six months. MSF started using delamanid in a compassionate use programme in January 2015.

"With the TB community waiting for new TB drugs for 50 years and more than 200,000 patients dying from MDR-TB every year, the very slow uptake of the new TB drugs is a scandal. Only by significantly scaling up the number of people diagnosed with drug-resistant tuberculosis, with all patients receiving treatment, will we see a drastic fall in the rate of new infections and deaths from this crisis.

DR JENNIFER COHN, MEDICAL DIRECTOR, MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN.


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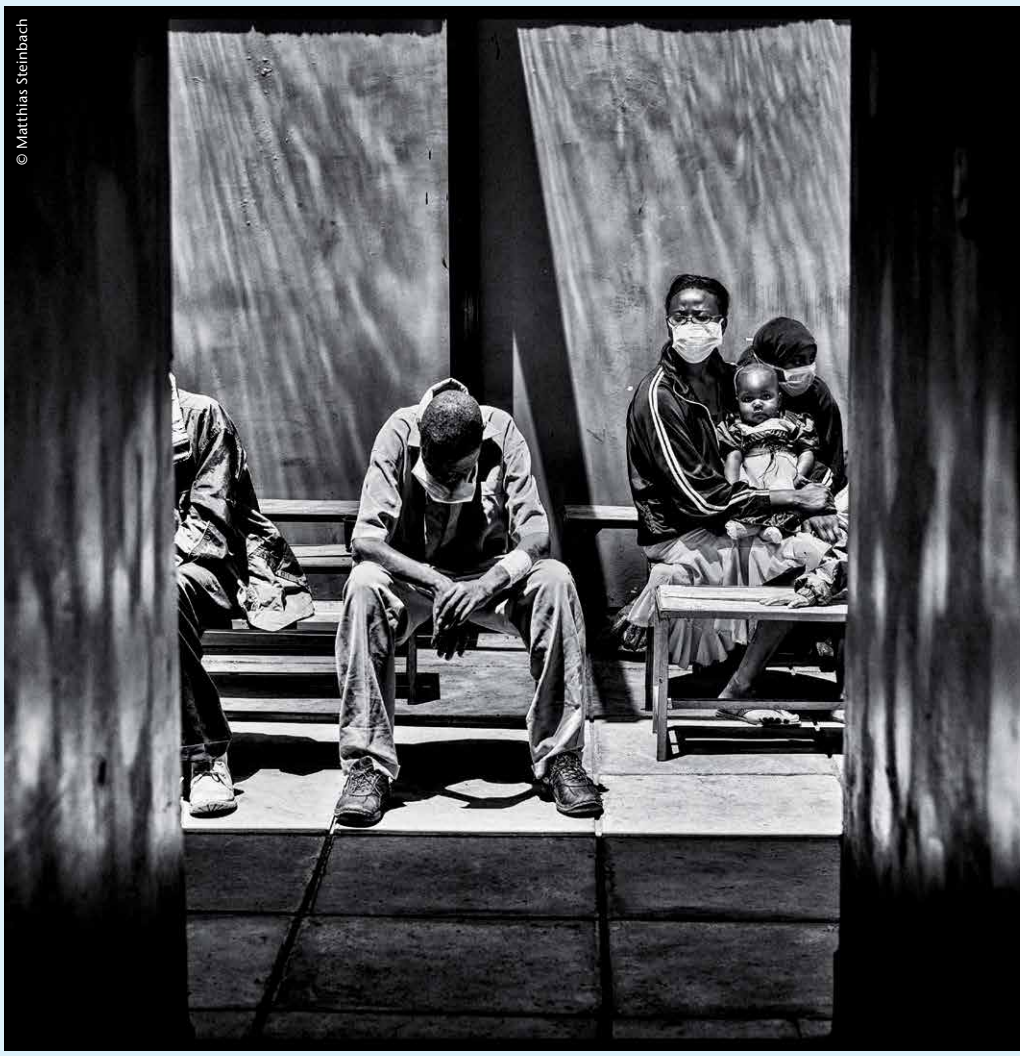
REPURPOSED DRUGS: PROMISING, BUT BARRIERS PREVENT WIDER USE

Linezolid (Pfizer) is an antibiotic that does not have a registered indication for TB. Further, the Pfizer price is prohibitive. Cheaper generic versions are becoming available; a version from Hetero is registered in the United Kingdom and one from Macleods is approved for temporary procurement by The Global Fund to Fight AIDS, Tuberculosis and Malaria. Four manufacturers (Teva, Mylan, Glenmark and Gate Pharma) received tentative approval from the US FDA, so these alternative sources should now become available. Many countries were previously unable to access low-cost versions due to Pfizer's patents, and secondary patents from Pfizer could present legal obstacles in some countries in the future. In South Africa, MSF is using linezolid as part of a regimen for patients diagnosed with pre-XDR and XDR-TB, but was paying approximately $65 per pill for the Pfizer product. After a long legal effort, MSF, thanks to an import waiver, has been granted permission to use Hetero's linezolid, which is 88% less expensive than the original, though still costly at $8 per pill. Following lengthy registration delays for generic versions of linezolid in South Africa, other treatment providers are now waiting for the Department of Health to announce plans for making generic linezolid more widely available.

Clofazimine (Novartis) is a drug that is used in the treatment of leprosy. It does not have an indication for TB, and Novartis, the originator company, severely restricts its use for TB. However, the use of clofazimine is increasing with its inclusion in the shortened nine-month MDR-TB regimen being tested in both the STREAM clinical trial and in operational research programmes. It is vital that clofazimine is registered for use in treating TB and that alternative quality-assured suppliers are found.

> *"Linezolid was the drug that helped me beat XDR-TB. But others did not have access to linezolid, and didn't survive. We need promising drugs like linezolid widely available at affordable prices to give more patients a better chance at a cure, because the treatments for DR-TB we have are so terrible, and don't always work.*
>
> **PHUMEZA TISILE, THE FIRST DR-TB PATIENT OFFERED A LINEZOLID-CONTAINING REGIMEN BY MSF IN KHAYELITSHA, SOUTH AFRICA.**



Imipenem/cilastatin is another antibiotic that is used in the treatment of XDR-TB. The drug comes at a high price, but widespread use in TB is likely limited in any case, due to its twice daily intravenous administration. MSF has been able to use the drug in our compassionate use programmes by inserting portacaths (long term intravenous access lines) for patients.

PATIENTS PRICED OUT OF THE EQUATION BY UNAFFORDABLE DR-TB DRUGS

The cost of each TB drug must be considered in the context of its contribution to the total cost of a regimen. TB programs are already struggling to scale-up access to today's $1,500-5,000 MDR-TB regimens. As evidence of new and repurposed drug efficacy in combinations grows, countries may face tough financial choices in trying to provide these more effective treatment regimens to patients in need. Middle-income countries in particular are disproportionally affected by high drug prices, as they shoulder the bulk of the global TB burden, but often have severely underfunded TB budgets. In the absence of robust market competition for these drugs, MSF suggests $500 per treatment course for low and middle-income countries as a reasonable price that could enable more countries to scale up life saving treatment.

MANUFACTURERS AND PRICES FOR NEW AND REPURPOSED TB DRUGS

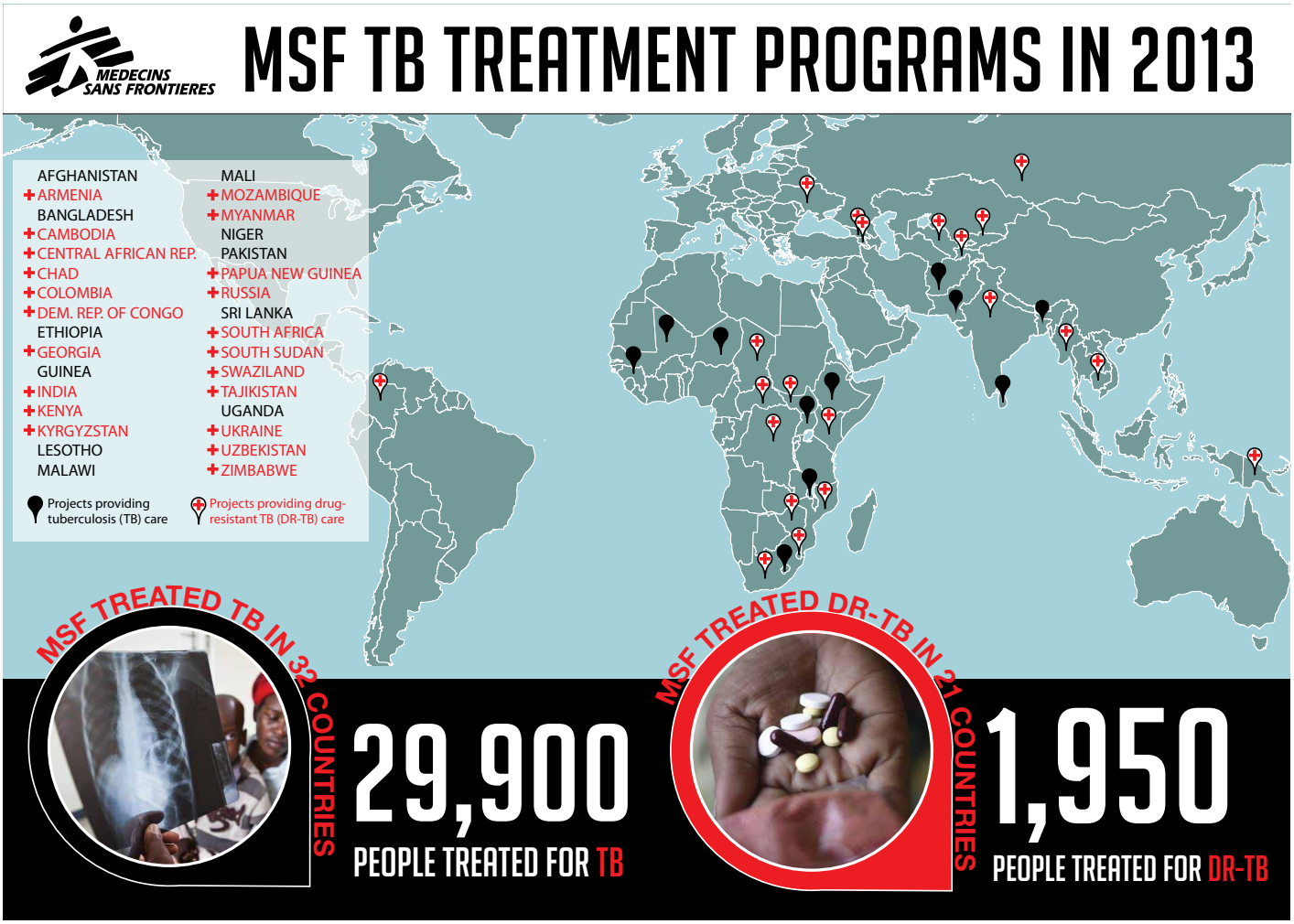
GROUP 5 DRUGS	**MANUFACTURERS & PRICE**	**GLOBAL DRUG FACILITY (GDF) POOLED PROCUREMENT** (prices valid until 31 March 2015)
BEDAQUILINE (Bdq)		
Approval status	Janssen: Stringent regulatory authority (SRA) approved	GDF Quality Assurance Policy
100mg tablet	Janssen: High-income: $159.97; upper middle-income: $15.96; least-developed/resource-limited countries: $4.79	Available for purchase, but price not public
CLOFAZIMINE (Cfz)		
Approval status	Novartis: SRA approved	GDF Quality Assurance Policy
50mg soft-gel capsule	Novartis: Price not available	$0.62 (Novartis via Pharmaworld)
100mg soft-gel capsule	Novartis: Price not available	$1.61 (Novartis via Pharmaworld)
DELAMANID (Dlm)		
Approval status	Otsuka: SRA approved	Not applicable
50mg tablet	UK: $78.00; Japan: $111.00	Not applicable
IMIPENEM/CILASTATIN		
Quality status	SRA approved	GDF Quality Assurance Policy
500/500mg vial, powder for injection	Demo, Labatec, Panpharma, MSD, Fresenius Kabi France	$7.32-10.64
LINEZOLID (Lzd)		
Approval status	Hetero & Pfizer: SRA approved	GDF Quality Assurance Policy
600mg tablet	Pfizer, Macleods: Price not available	$6.90 (Hetero)
100mg/ml suspension powder	Pfizer: Price not available	Not applicable

CHALLENGES IN ACCESSING NEW AND REPURPOSED TB DRUGS

DEVELOPMENT STAGE	ACCESS BARRIERS	WHAT NEEDS TO HAPPEN
Bedaquiline (Bdq), *Janssen*		
- Accelerated approval from US FDA, conditional approval from EMA, full approval in the Russian Federation, South Africa, India, Peru, Philippines, South Korea, Turkmenistan, Khazakstan; all based on phase IIb data. - Phase III in planning - Recommended by WHO for use in adult patients with MDR-TB, subject to five conditions	- Price: $900 for low-income countries (LICs), $3,000 for middle-income countries (MICs) for a six-month course as well as costly pharmacovigilance requirements - Intellectual property barriers (compound and multiple secondary patents) until 2029 that limit generic competition or development of fixed dose combinations - Delays in registration with multiple National Medicine Regulation Authorities (NMRAs) - Little data on use with other new TB drugs (e.g. delamanid) - Submission under evaluation for the WHO Essential Medicines List (EML)	- Access to a more affordable price, especially for MICs - Additional details of USAID/Janssen donation programme shared with the public - Reduction of intellectual property barriers through use of TRIPS flexibilities or voluntary licensing - High burden TB countries' NMRAs must prioritise registration - Inclusion on the WHO EML - Rapidly commence trials looking at combining bedaquiline with other new drugs and in shorter regimens - Use of CU or other in-country waiver processes
Clofazimine (Cfz), *Novartis*		
- Registered for use in treating leprosy. - Recommended by WHO as a Group 5 drug for TB treatment	- Does not have an indication for TB - Only one quality-assured manufacturer makes this drug and quantities may not be sufficient for scale up of clofazimine-containing regimens, including new shortened regimens - Not yet included in the WHO EML for TB	- Novartis and future generic manufacturers should pursue obtaining a TB indication for clofazimine - Tech transfer for API production to allow sustained availability; prioritize reformulation to a presentation more suited to hot and humid environments, allowing for dosing adaptation - Current and future generic manufacturers of active pharmaceutical ingredient and finished product of clofazimine should pursue WHO prequalification - Inclusion on the WHO EML for TB
Delamanid (Dlm), *Otsuka*		
- Full approval by EMA, and PMDA in Japan, based on phase IIb data. Phase III finished enrolling - Recommended by WHO for use in adult patients with MDR-TB, subject to five conditions	- Global price strategy is not yet known. The price for a 6-month course is $28,000 in the UK and $40,000 in Japan - Only currently registered in the European Union, Japan and South Korea - Intellectual property barriers (compound and secondary patents) until 2031 that limit generic competition or development of fixed dose combinations - No proactive plans to register in high-burden TB countries or trial countries - Little data in use with other new TB drugs (e.g. bedaquiline) - Submission under evaluation for the WHO EML	- Pricing for L&MICs must be affordable and enable access - Reduction of intellectual property barriers through use of TRIPS flexibilities or through voluntary licensing - Otsuka must urgently register delamanid in high-burden TB countries and trial countries; in the meantime, delamanid should be accessible through CU programmes more broadly - Increased transparency from manufacturer on price and registration questions - Inclusion on the WHO EML - Rapidly commence trials for combining delamanid with other new drugs and in shorter regimens
Linezolid (Lzd)		
- Registered for use in treating resistant infections caused by typical bacteria. - Recommended by WHO as a Group 5 drug for TB treatment	- Does not have an indication for TB - Intellectual property barriers (secondary patents) that could preclude importation of low-cost generics until 2021 in some countries - Despite the entry of two generic manufacturers (Hetero, Macleods), price remains an issue - Submission under evaluation for the WHO EML for TB	- Pfizer, Macleods or Hetero should register linezolid in all high burden TB countries as a priority - Pfizer, Macleods and Hetero should pursue a TB indication for this drug - Price reductions to improve affordability - Use of TRIPS flexibilities, if needed, to remove remaining secondary patents in countries where treatment scale up is needed - Inclusion on the WHO EML for TB
PA824, *TB Alliance*		
- In Phase II development. Phase III trial planned (STAND-TB)	- As it will not be registered as a single drug, important that it is made available for development of drug combinations beyond those currently being trialled - No plans for CU	- Review possibility of allowing access to PA824 for CU as soon as Phase II trials are successfully completed - Allow access to PA824 for use in trials combining it with other new drugs and additional shorter regimen trials

MSF: EFFORTS TO EXPAND AND IMPROVE TREATMENT FOR DR-TB

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



The endTB Consortium

MSF is part of the endTB constorium, along with Partners in Health (PIH) and Interactive Research & Development (IRD), which is being set up with the support of and in collaboration with UNITAID. The aim of the endTB project is to obtain increased uptake of new TB drugs as part of treatment regimens that are shorter, more effective and less toxic, through: improved evidence on the safety & efficacy of new TB drugs, accelerated uptake of new drugs (short-term) and regimens (long-term) in endTB countries, and broader evidence-based WHO recommendations for use of new TB drugs and regimens.

Six hundred MDR patients will be enrolled in the clinical trials, and 2,600 MDR-TB patients will be enrolled on treatment with new drugs, including bedaquiline and delamanid.

The endTB treatment sites will be in 16 countries, 13 of which are among the list of 30 countries with the highest burdens of MDR-TB. In most countries, PIH, MSF, or IRD will directly implement endTB activities. In all countries, PIH, MSF or IRD will work closely with the National TB Programs and other national authorities.

ENSURING A HEALTHY PIPELINE: RETHINKING TB DRUG RESEARCH AND DEVELOPMENT

Research and development of TB drugs suffers from significant weaknesses throughout all stages of development, hampering the development of new regimens. The way TB drug research is done today is not adequately responding to the needs of patients and TB programmes. With chronic underfunding and major pharmaceutical companies withdrawing or reducing their investment in TB R&D, novel approaches must be considered to re-energise the pipeline, bring new funders to the arena, prioritise regimen development early in the drug development process, and ensure access and affordability for products.

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

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

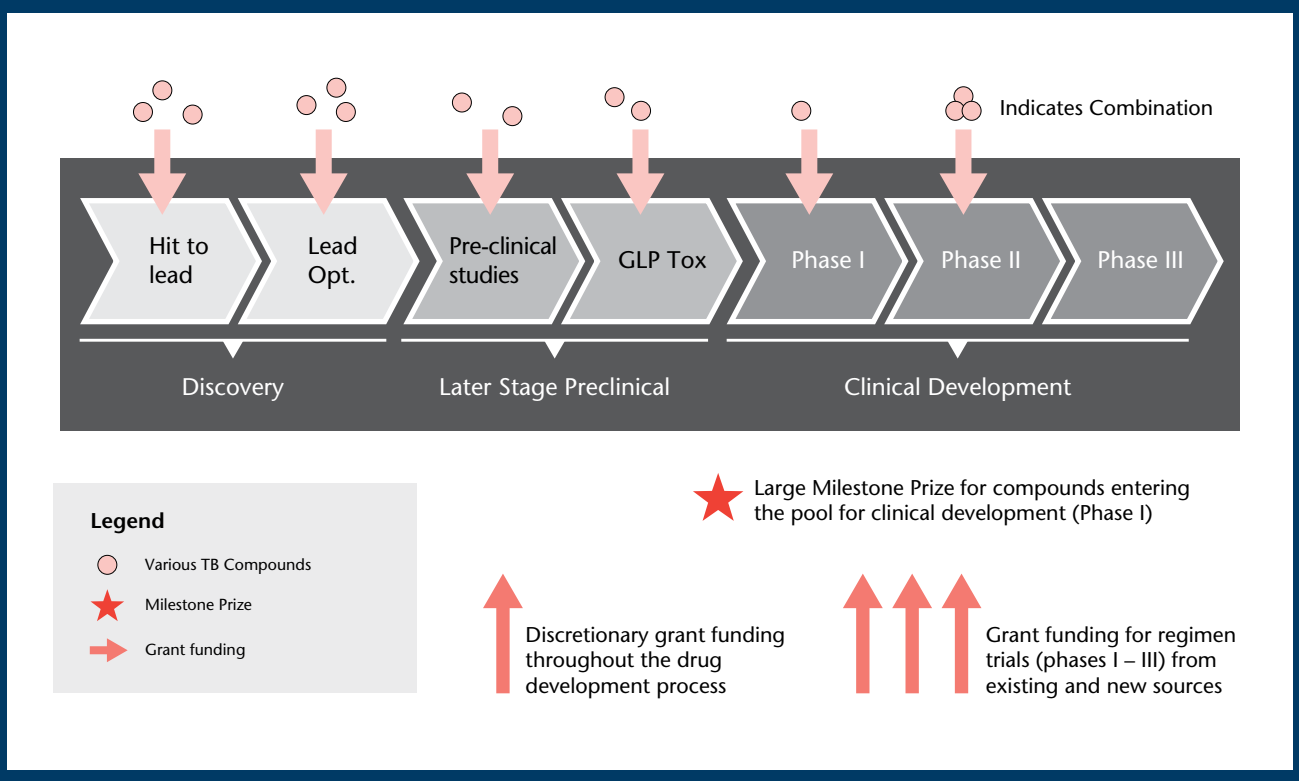
Push funding to finance R&D activities upfront (i.e. through grants);

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

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

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

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



RECOMMENDATIONS:
MSF URGES IMMEDIATE ACTION TO INCREASE ACCESS TO LIFESAVING DR-TB DRUGS

TB-ENDEMIC COUNTRIES:

Ensure national TB treatment guidelines, Standard Treatment Guidelines and Essential Medicines Lists are regularly updated in line with WHO guidance, including for Group 5 medicines; enact procedures that allow importation and dispensation of quality-assured Group 5 medicines not yet registered; implement the necessary legislation for CU; proactively reach out to quality-assured manufacturers, enabling fast track registration for priority TB medicines; recognize market authorisations granted by stringent National Medicine Regulation Authorities, and make use of international regulatory flexibilities such as the collaborative registration process at the WHO prequalification programme.

WORLD HEALTH ORGANIZATION:

Ensure all DR-TB medicines, including new compounds, are added onto the WHO EML and the Expression of Interest of WHO Prequalification Programme; issue timely interim guidance for new compounds and regimens and update final treatment guidelines; give guidance to countries on initiating CU programmes and facilitating fast track registration of the new compounds and new regimens; support countries in their use of the collaborative registration process at WHO prequalification programme and make attempts to expand this process to stringent NMRAs.

MANUFACTURERS [SEE 'CHALLENGES IN ACCESSING NEW AND REPURPOSED TB DRUGS' CHART]:

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

DONORS:

All donor and middle-income countries should step up political and financial commitment and support scale-up of new treatments, by promoting the exclusive use of quality-assured TB medicines; and consider long-term innovation and access strategies, through support for the creation of the 3Ps Project (see msfaccess.org/push-pull-pool).

GLOBAL HEALTH ACTORS:

In March 2015, MSF and 88 other organizations sent a letter to key global health actors in the TB community requesting the formation of a consortium, which would dedicate itself to meeting time-bound concrete goals for scale-up of DRTB treatment. These include:

- **Quickstart:** Ensure 500 patients are started regimens which include BDQ by July 2015, and 500 patients started on regimens which include DLM by January 2016.
- **Optimal DR-TB treatment:** Provide technical assistance for implementation plans for top 25 endemic countries by 2016; ensure BDQ and DLM are part of routine treatment in 20 countries by end of 2016 and 52 countries by end of 2019; and that key repurposed drugs are in use by the national TB programmes.
- **Regulatory status:** BDQ and DLM dossiers are submitted for registration in 25 countries by beginning of 2016 and 52 countries by 2017; and drugs are registered, or import waivers are in place, by 2016.

ADDITIONAL MSF RESOURCES DR-TB

- **Call to action:** Accelerating access to DR-TB drugs – msfaccess.org/52pickup
- **Out of Step:** Deadly implementation gaps in the TB response – msfaccess.org/outofstep
- **Under the Microscope:** Sources and prices for drug-resistant tuberculosis medicines – msfaccess.org/utm2013
- **Beyond the Microscope:** Addressing the critical need for better TB diagnostics – msfaccess.org/content/beyond-microscope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