DR-TB DRUGS UNDER THE MICROSCOPE

SOURCES AND PRICES FOR DRUG-RESISTANT TUBERCULOSIS MEDICINES

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THE MSF ACCESS CAMPAIGN

In 1999, in the wake of Médecins Sans Frontières (MSF) being awarded the Nobel Peace Prize, MSF launched the Access Campaign. Its sole purpose has been to push for access to, and the development of, life-saving and life-prolonging medicines, diagnostics and vaccines for patients in MSF programmes and beyond.

MSF has been involved in TB care for 25 years, often working alongside national health authorities to treat patients in a wide variety of settings, ranging from urban slums to rural areas, prisons and refugee camps. MSF's first MDR-TB programmes opened in 1999, and the organisation is now one of the biggest NGO providers of MDR-TB care.

In 2011, the organisation treated 26,600 patients with TB in 39 countries, 1,300 of whom had MDR-TB. Overall the success rate of treating MDR-TB within MSF is 53% and only 13% in XDR-TB patients.

THE INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE

The mission of the International Union Against Tuberculosis and Lung Disease ('The Union') is to bring innovation, expertise, solutions and support to address health challenges in low- and middle-income populations. With nearly 10,000 members and subscribers from 150 countries, The Union has its headquarters in Paris and offices serving the Africa, Asia Pacific, Europe, Latin America, Middle East, North America and South-East Asia regions. Its scientific departments focus on tuberculosis and HIV, lung health and non-communicable diseases, tobacco control and research.

The Union has been the leading international TB control and prevention agency since 1920. Each year, The Union works in close to 90 countries, providing technical assistance at the request of national tuberculosis control programmes; conducting operational research and clinical trials; organising conferences and courses; and publishing not only two peer-reviewed journals, but also a range of technical guides.

In addition, The Union regularly monitors MDR-TB project sites and provides technical assistance on all aspects of MDR-TB management in Europe, Africa, Asia, Latin America and the Middle East. The Union organises also comprehensive clinical MDR-TB courses in Africa, Asia and Latin America, as well as more than 15 national courses including most of the high-burden MDR-TB countries.

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DR-TB DRUGS
UNDER THE MICROSCOPE

Tuberculosis (TB) is a curable disease that continues to kill nearly 1.4 million people across the globe each year, and is the main cause of death in people living with HIV/AIDS. In 2011, there were up to an estimated 400,000 cases of multidrug-resistant TB (MDR-TB) among notified TB patients; MDR-TB is a form of the disease that does not respond to at least two of the primary drugs used to treat the disease. Close to 10% of all MDR cases are in fact extensively drug-resistant (XDR-TB), meaning they are also resistant to two of the key drugs used as a part of second-line regimens.[1]

Yet the response to the epidemic remains inadequate. With 94% of patients at risk of MDR-TB (those previously treated) not having access to tests capable of diagnosing MDR-TB, and only 19% of people with MDR-TB having been enrolled on treatment in 2011, the full extent of the burden is unknown and undertreated. The Global Drug Facility – the international pooled procurement mechanism for TB medicines and diagnostics – procured DR-TB treatments for less than 20,000 people in 2011.[2]

Given this alarming outlook, it is imperative that DR-TB be considered a public health emergency, one that mobilises an appropriate response from all stakeholders, including governments, the World Health Organization (WHO), the private sector, donors, civil society organisations, and affected communities.

Treating DR-TB is complex: medicines need to be taken for two years, and regimens need to be tailored to the individual patient, based on which drugs are effective against that person's infection. Side effects are severe and incapacitating, so much so that programmes must devote considerable resources to adherence counselling, managing side effects and providing psychosocial care. From the programmatic perspective, significant investments are required. Resources are needed, in human resources and training, investment in laboratory infrastructure to diagnose infection and monitor treatment, as well as ensuring adequate infection control measures are taken. These challenges, although considerable, lie beyond the scope of this report.

This report focuses on just some of the many factors that hamper the scaling up of DR-TB treatment – the limited availability and high cost of quality-assured medicines for resistant strains of the disease, owing to an insecure market and insufficient demand; and the research questions that remain unsolved with existing medicines.

Finally, as the R&D pipeline prepares to deliver the first new compounds for TB in close to half a century, the report provides an initial assessment of the approaches to be taken in order to radically transform our ability to respond to this plague.


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DR, MDR, XDR: THE MANY FACES OF RESISTANT TB

Drug-resistant tuberculosis (DR-TB) is used to describe strains of TB that show resistance to one or more first-line drugs.

Multidrug-resistant tuberculosis (MDR-TB) is defined by TB that is resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs.

Extensively drug-resistant tuberculosis (XDR-TB) is caused by strains of MDR-TB that are also resistant to second-line drugs, including at least one from the class of fluoroquinolones, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).

The phrase 'totally drug-resistant TB' has been used since late 2010 to describe a group of patients in India that have developed resistance to all drugs for which they were tested. However, this is not accepted WHO terminology, and these cases are officially defined as XDR-TB.

All forms of resistance to more than one of the first-line drugs, and which are neither MDR-TB nor XDR-TB, are defined as polydrug-resistant TB (PDR-TB).

HOW MARKET INSECURITY IMPACTS PRICE AND QUALITY

DR-TB MEDICINES ARE EXPENSIVE

Medicines are far from being the only cost associated with treating DR-TB. Programmes must devote considerable resources to adherence counselling, managing side effects and providing psychosocial care, to infection control and laboratory support.

The price of medicines adds to these costs. Whereas first-line TB treatment is affordable, costing only US$22 per patient for a six-month treatment course,[1] DR-TB treatment is considerably more expensive.

The exact price varies considerably, as treatment must be individualised according to a patient's drug resistance profile. But the cost of a standard regimen for MDR-TB as recommended by the 2011 WHO treatment guidelines, lasting 24 months and with eight months of injectable capreomycin, ranges between $4,000 and $6,000.

Four medicines in particular weigh heavily in the overall cost of a DR-TB regimen: capreomycin, moxifloxacin, PAS and cycloserine. Using kanamycin instead of capreomycin brings the price down, but at $2,850, the cost of the medicines is still too high.

TABLE 1:

The cost in US$ of a standard MDR-TB regimen lasting 24 months, including cycloserine and eight months of injectable capreomycin, using quality-assured medicines, based on prices provided for this report.

MEDICINE	LOWEST QUALITY-ASSURED PRICE		HIGHEST QUALITY-ASSURED PRICE	
	Unit price	Cost for regimen	Unit price	Cost for regimen
capreomycin 1gr vial	5.34	1,281.6	8	1,920
cycloserine 250mg caps	0.58	1,252.8	0.8	1,728
ethionamide 250mg tab	0.07	151.2	0.1	216
moxifloxacin 400mg tab	1.68	1,209.6	1.85	1,332
pyrazinamide 400mg tab*	0.02	57.6	0.02	57.6
Total regimen cost		**3,952.8**		**5,253.6**

*Price sourced from the GDF online catalogue at http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

TABLE 2:

The cost in US$ of a standard MDR-TB regimen lasting 24 months, including PAS and eight months of injectable capreomycin, using quality-assured medicines, based on prices provided for this report.

MEDICINE	LOWEST QUALITY-ASSURED PRICE		HIGHEST QUALITY-ASSURED PRICE	
	Unit price	Cost for regimen	Unit price	Cost for regimen
capreomycin 1gr vial	5.34	1,281.6	8	1,920
PAS / PAS Sodium	1.45	2,088	1.57	2,260.8
ethionamide 250mg tab	0.07	151.2	0.1	216
moxifloxacin 400mg tab	1.68	1,209.6	1.85	1,332
pyrazinamide 400mg tab*	0.02	57.6	0.02	57.6
Total regimen cost		**4,788**		**5,786.4**

*Price sourced from the GDF online catalogue at http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

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THE MARKET IS SMALL AND FRAGMENTED

For most DR-TB drugs, with the notable exceptions of linezolid and moxifloxacin, the medicines were developed so long ago that patents, which typically act to prevent competition and thereby keep prices higher for longer, have long run out, and do not act as a barrier.

These high prices are rather a reflection of the fact that current market demand is low, due to limited capacity to diagnose and treat DR-TB, which does not provide a sufficient incentive to manufacturers. The global DR-TB market was estimated to be worth $300 million in 2010, with only $125 million procured through the public sector.[3]

Considering the current capacity to diagnose and treat DR-TB is limited, the small international market size is not appealing for manufacturers. Furthermore, there is still a high degree of variation between regimens used by country programs, which leads to a very fragmented market. For example, there is no general consensus between the use of ethionamide or prothionamide, between cycloserine or terizidone, nor between capreomycin or other injectable drugs. Even packaging requirements for DR-TB drugs differ between India and the rest of the world.

As a result of these factors, manufacturers can not achieve economies of scale necessary to bring prices down. Although greater market competition among multiple producers could help, the impact would be limited; indeed the greater challenge today is securing today's fragmented and fragile market. Securing greater demand is therefore critical to bringing prices down.

UNCOVERING THE EPIDEMIC OF DR-TB

While timely and accurate diagnosis of DR-TB remains a significant challenge for most high-burden countries, recent diagnostic advances provide a key opportunity to significantly improve diagnosis of DR-TB and increase demand for DR-TB medications. Introduction of nucleic acid amplification (NAA)-based tests, such as Xpert MTB/RIF, are expected to result in a three-fold increase in the diagnosis of DR-TB[4] and to significantly decrease time to DR-TB treatment initiation (detection of TB and drug resistance takes about two hours with Xpert MTB/RIF, as opposed to more than four weeks for conventional culture and drug sensitivity testing).

Improving access to DR-TB diagnosis through Xpert MTB/RIF, optimizing its operating characteristics, and ensuring access to confirmatory tests – including culture, phenotypic drug sensitivity testing and line probe assay – are key to uncovering the epidemic of DR-TB. Moving forward, developing more robust and less sophisticated next-generation NAA-based tests which are better suited to resource-limited environments, will also be crucial.

New tools must be developed that will be less expensive, and will allow diagnosis of paediatric or extra-pulmonary tuberculosis using a range of sample types. Finally, a point of care TB diagnostic test suitable for implementation in most peripheral settings is also critical to ensuring adequate access to TB diagnosis in settings where the majority of patients are seen. But such a test is still not available and research efforts should be focused on achieving this important tool.

SUPPLY OF QUALITY-ASSURED SOURCES IS INSECURE

The modest market size also has an effect on the security of supply of quality-assured sources.

Compared to the first edition of this report, published in March 2011, the overall situation of DR-TB drugs has slightly improved with more sources of quality-assured drugs now available for procurement for TB treatment. Three manufacturers have been approved by the WHO Prequalification Programme for ofloxacin, two manufacturers for levofloxacin and one source of PAS-Sodium. Others are in the process of having their products evaluated by WHO. The joint Global Drug Facility / Global Fund Expert Review panel, an additional mechanism for assessment of drug quality, gave temporary purchase permission for two sources of prothionamide, one of moxifloxacin, one of ethionamide, one of levofloxacin and one of cycloserine.

A few other sources have received marketing authorisation by a stringent regulatory authority.

Nevertheless, the situation remains fragile and supply is vulnerable for the market of quality assured DR-TB medicines. Thirty per cent of drugs profiled in this report – kanamycin, terizidone, clofazimine and linezolid – are still reliant on only one supplier. Even drugs for which at least two suppliers are available, are often reliant on the same manufacturer for the active pharmaceutical ingredient. For all of these medicines, supply is extremely vulnerable to disruption.

The past example of kanamycin illustrates the risks associated with relying on too few sources for a given medicine. Several manufacturers had kanamycin registered for use in the US, although all but one subsequently ceased production, because of falling demand in wealthy countries. Of three quality-assured sources of kanamycin globally, the first was forced to suspend production because its active pharmaceutical ingredient (API) supplier relocated in 2009. The second also experienced a supply problem in 2010 and ceased production for a period of time, leaving programmes dependent on a third manufacturer with limited capacity, so much so that the manufacturer dedicated its production solely to GDF procurement, which left other DR-TB treatment programmes with no quality-assured source. While this situation is now resolved, this experience serves as a cautionary tale.

Sources of API are also limited. A 2010 study for the GDF noted that the supply of API was vulnerable for amikacin, kanamycin, prothionamide and clofazimine.[5]

GETTING MEDICINES INTO BODIES: ADDITIONAL DIFFICULTIES

There are additional barriers faced by treatment providers to getting drugs into countries and to patients.

One is lead times. Orders for DR-TB drugs placed with GDF are often small and need to be pooled by manufacturers before they produce a new batch, leading to four to six months standard lead times, from order placement to receipt in country. In order to overcome this challenge, UNITAID has financed a stockpile so that more expedited shipments can be organised by GDF. In 2011, this stockpile was used by 60 national tuberculosis programmes and served mainly to complement orders for which quantities were missing. Twenty national tuberculosis programmes placed 25 emergency orders in 2011, which were delivered with a median lead time of 31 days.[6] Unfortunately, 25 emergency orders with expedited delivery represent only a small proportion of GDF orders.

The lack of a streamlined process between forecasting needs at country level, cost evaluation and planning of orders, the signature of agreements, and disbursements of donor funds all contribute to making lead times for DR-TB drug delivery excessively long. National TB programmes also need to fully pre-pay their orders before they can be processed by GDF. If agreements with donors and consequent disbursements are delayed, the process is blocked. A revolving fund mechanism where money could be advanced to countries before donors funds are made available could alleviate this road-block.

Delays are also largely caused by national regulations: as DR-TB drugs are often not registered in countries where treatment projects are located, MSF experience shows that cumbersome special authorisation is frequently needed to import them. Additionally, many countries do not fast-track registration procedures for medicines that have been quality-assured through the WHO Prequalification Programme.

Finally, for some DR-TB drugs, additional barriers prevent them from reaching the DR-TB patients. Neither linezolid nor clofazimine have an approved indication for DR-TB. Access to clofazimine for the treatment of XDR-TB patients has been denied on the basis of unclear efficacy,[2] while linezolid is extremely expensive. As a result, while there is one quality-assured producer for both, accessing these drugs at an affordable price is extremely difficult. For more details refer to the drug profiles for these medicines.

ADDRESSING THESE CHALLENGES

By diagnosing patients more effectively and more quickly with DR-TB, new diagnostic tests have the potential to increase demand for DR-TB drugs by helping expose the true scale of the crisis.

Aside from stimulating demand and encouraging countries to scale up treatment, other avenues should be explored:

POOLED PROCUREMENT

By aggregating individual countries' demand, pooled procurement has the potential to bring a global solution to problems of supply disruption of API and/or finished formulations.

Today, the Global Drug Facility (GDF) acts as a procurement mechanism for DR-TB drugs by pooling demand generated through DR-TB programme grants made by the Global Fund to Fight AIDS, Tuberculosis and Malaria. In 2010, $40 million was channelled through this pooled procurement mechanism for TB medicines and diagnostics.[7] Since 2011, securing approval from the Green Light Committee ceased to be a pre-condition for procuring DR-TB drugs through the GDF. Countries now have the possibility to procure partial regimens through the GDF, with the commitment from the countries that GDF drugs are used only in conjunction with quality-assured drugs. In parallel, regional GLC offices have been concentrating on monitoring and technical assistance in countries and are still involved in the approval process of Global Fund-funded programmes.[2]

In a fragmented and volatile market, pooled procurement could facilitate global solutions to supply disruptions, as very few countries have the capacity or resources to identify new sources of quality-assured medicines on their own. However, a pooled procurement mechanism on its own will not secure and maintain a market of affordable quality-assured drugs, unless the size of the demand it covers is substantial.

"It's the collective responsibility of the TB community to act so that patients can get access to better treatment soon. The Union is trialling a shorter treatment regimen for MDR-TB. Other actors also need to act, and with two new drugs active against TB potentially reaching the market in 2013 – the first in decades – it needs to happen now."

Christophe Perrin, Pharmacist, International Union Against Tuberculosis and Lung Disease

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THE ROLE OF MIDDLE-INCOME COUNTRIES

With the market for DR-TB drugs largely concentrated in the BRICS countries – Russia, India and China account for 60% of all notified DR-TB cases among the 22 high-burden countries – procurement decisions made in these countries will have a considerable impact on the future shape of the market.[1] If they committed to using DR-TB medicines that meet WHO quality standards, global demand for these would be consolidated, likely leading to more quality-assured suppliers of both API and finished formulations entering the market.

These countries also play a major role in manufacturing of both API and finished formulations. 80-85% of active pharmaceutical ingredients, including for second-line drugs, are produced in China, largely due to its advanced fermentation technology and cost position for manufacturing.[8] India is a major producer of finished TB formulations. Yet not all medicines produced and marketed in these countries meet WHO standards.[9, 10]

Exposing large numbers of TB patients to non-quality-assured medicines represents a serious threat to public health. Several initiatives have been undertaken to address this threat and promote quality-assured DR-TB drugs in these countries, whether in terms of production or procurement. For example, since 2009, initiatives and technical assistance aimed at boosting the production of quality-assured TB medicines in China have been undertaken,[11, 12, 13] but government commitment is additionally needed to increase access to quality-assured TB treatment. While in Brazil, the government has shown strong political will to control the TB drug market, with drugs to treat both drug-sensitive and drug-resistant TB available solely in the public sector, and free of charge.[14]

In other countries, however, TB and DR-TB drugs are not channelled through TB programmes and their dispensing is not regulated. In India, for example, drugs to treat both drug-susceptible TB and DR-TB are available over the counter in the private market.[15] Patients are left to purchase such drugs out of pocket, often not able to afford the all drugs in the regimen or the full treatment course, which can have a hugely negative impact, fuelling further drug resistance.

CREATING INCENTIVES FOR MANUFACTURERS

Part of the problem of too few quality-assured sources for international supply could be resolved by linking funding to procurement for quality-assured medicines. While the Global Fund requires the drugs procured by the DR-TB programmes it funds to meet WHO quality standards, thus contributing to pooled demand for quality-assured medicines, other donors such as the World Bank do not set specific quality criteria.

When weak regulatory authorities allow marketing of products that do not meet WHO quality standards but are nevertheless procured by national tuberculosis programmes, drug quality is clearly not being prioritised enough. Efforts should also be directed at manufacturers to encourage them to improve compliance with internationally recognised quality standards and submit product dossiers for quality assessment through the WHO Prequalification Programme or stringent regulatory authorities. To date, institutions, governments and WHO have not done enough in this regard.

One welcome step is that the GDF has had a clear quality assurance policy since 2010 that sends a signal to manufacturers to invest in quality, by requiring products to be either quality-assured by the WHO Prequalification Programme, a stringent regulatory authority (SRA), or to be approved by the GDF/Global Fund's Expert Review Panel. The Panel provides time-limited approval for products that have fewer than three sources approved by either the WHO Prequalification Programme or SRA.

The GDF has now published an overview of prices online;[16] they have also provided further information on products used for the purpose of this publication, helping to increase price and quality transparency.

> "Alarmingly, in some of our clinics in Central Asia, up to one third of patients who have TB for the first time are coming in with strains that are already drug-resistant. While we've been able to scale up treatment modestly within our projects, we struggle every day with the inadequate tools and drugs to tackle the disease. With two new drugs coming to market in the next year, we have a historic opportunity to improve DR-TB treatment. These drugs need to be introduced effectively, so governments and treatment providers can scale up the response to this alarming crisis."
>
> **Dr Teshome Ashagre**,
> Medical Coordinator,
> MSF Uzbekistan

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Addressing these challenges continued

"Multidrug-resistant tuberculosis is an escalating public health emergency, yet the global response is abysmal, with levels of testing and treatment remaining shockingly low. With barely one in twenty TB patients being tested for drug resistance, we're just seeing the tip of the iceberg. Even if you are diagnosed and lucky enough to receive treatment for drug-resistant TB, it is appalling that you only have a 48% chance of being cured. We need more testing, we need more treatment and we need better drugs to make treatment more effective and more tolerable for patients"

Dr Grania Brigden,
TB Advisor for Médecins Sans Frontières' Access Campaign

SECURING THE FUNDING BASE

Funding will also be required in order to consolidate the market and respond to the demand for DR-TB drugs. Overall, domestic funding accounts for 86% of total funding for TB control, with the Global Fund accounting for 12% and grants from other agencies for 2%.[17]

The value of grants for DR-TB from the Global Fund is progressing, and reached $130 million in 2011. According to country reports, the biggest grants are for India and China, at $36 million and $31 million respectively.[17] When only international funding is taken into consideration, the Global Fund's share represents 82% of the total spent – a figure that rises to 91% for MDR-TB.[17] The Global Fund remains the predominant international donor for access to DR-TB treatment.

As a consequence, the financial woes at the Global Fund – which led to the agency having to cancel its 11th funding round in November 2011 – may lead to more restrictive grant-making for DR-TB. Additional restructuring at the Global Fund may further restrict the amount of funding available for TB grants and also risks severely cutting the amount of money available to the BRICS countries, where most DR-TB occurs. Although DR-TB is included among the essential services to be funded under the 'Transitional Funding Mechanism'[18] that was set up to ensure the continuation of grants, the list of countries eligible for future grants has been restricted, with middle-income countries with high MDR-TB burdens at high risk of cuts in Global Fund support. Any future changes in the Global Fund need to take into account the huge costs of scaling up MDR-TB care and ensure there are adequate funds allocated to addressing this.

This vulnerability comes in a context of considerable need: WHO estimates that an additional $3 billion are needed each year to fill the funding gap for TB care, a figure which does not even include the research and development needs.[19]

RESEARCH AND DEVELOPMENT: NEEDS AND OPPORTUNITIES

NEGLECTED POPULATIONS: CHILDREN AND PEOPLE LIVING WITH HIV/AIDS

To date, there has been very little research to even determine the best use of existing DR-TB drugs, with today's DR-TB treatment largely based on experience and expert opinion rather than randomised clinical trials, and many 'grey areas' where expert opinions may be conflicting.

Children are particularly neglected. At least 10-15% of total TB cases each year occur in children, and a similar percentage can be assumed among new DR-TB cases in children.[20] Yet the WHO programmatic guidelines released in 2011 did not provide guidance on dosing and use of DR-TB drugs in children and adolescents. And only three medicines featured in this report (amikacin, levofloxacin and linezolid) have been developed as paediatric formulations. These are not widely available, with none included in the GDF product catalogue, which means that treatment providers cannot purchase them through the GDF. Treatment providers who attempt to treat children therefore must do so by manipulating adult formulations, such as breaking or crushing tablets to approximate the required dose. This carries a major risk of over- or under-dosing a child.

In addition, safety and efficacy data in children have not been established for the majority of the medicines used in DR-TB treatment. Only three medicines in this report have been licensed for use in children. However one of those that is licensed for paediatric use, levofloxacin, has not been approved beyond 14 days of treatment, even though a child with DR-TB would need to take the medicine for close to two years.

The interactions of DR-TB drugs with HIV medicines are also largely unknown.[21] This research has not been a priority for HIV drug developers because co-infection with TB is now uncommon in wealthy countries. This is particularly problematic given that TB is the biggest killer of people living with HIV today.[22]

For many DR-TB medicines, crucial research is lacking. For kanamycin, amikacin and capreomycin, for example, the potential for renal toxicity when used with tenofovir (the backbone of the WHO-recommended first-line HIV treatment regimen) is unstudied. The medicines of the fluoroquinolone class – moxifloxacin, levofloxacin and ofloxacin – are thought to interact with crucial protease inhibitors like lopinavir and atazanavir (both part of second-line HIV regimens). Drug interactions are also predicted between ethionamide and prothionamide and ARVs such as nevirapine and efavirenz. And there is very little knowledge about possible interactions for other medicines, such as cycloserine, terizidone and PAS.

FINALLY SOME GOOD NEWS AFTER A HALF CENTURY OF NEGLECT

With treatment that is expensive, complex, toxic and, with success rates at around just 50%,[23] insufficiently effective, many look to the research and development (R&D) pipelines for a new regimen to address these problems.

R&D into TB drugs and diagnostics has been neglected for decades because the disease primarily affects developing countries and therefore does not represent a lucrative market for the pharmaceutical industry.

Compared to other disease treatment pipelines, TB's drug pipeline remains fairly limited. But after nearly a half century of neglect, there is encouraging progress in recent years, with ten drugs in clinical testing (four repurposed, six new drugs and three new classes of drugs).[24] Most encouragingly, two completely new compounds – bedaquiline and delamanid – have been submitted for approval for MDR-TB treatment by stringent regulatory authorities, the first for TB in half a century.

There is an unprecedented opportunity to start building a new approach to treating DR-TB. How these drugs are used will be critical in that respect: will they be added to the existing regimen to optimise outcomes, or can entirely new regimens be devised?

Access to these promising drugs should be accelerated in a way that improves the effectiveness, shortens the duration and reduces adverse effects of the current M/XDR-TB treatment regimen. There is an opportunity to develop one or more regimens that achieve these goals as well as addressing the programmatic barriers that the current treatments pose to implementers.

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CLINICAL TRIALS, ONGOING AND PLANNED

Clinical trials are being run with existing drugs to shorten the duration of today's MDR-TB treatment. The Union, for example, is sponsoring the Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis drugs for patients with MDR-TB (STREAM) trial, which will assess a nine-month standardised treatment regimen for MDR-TB that achieved excellent outcomes with a cure rate of 87% in a non-randomised observational study in Bangladesh.[25] Modelled on the Bangladesh regimen, the STREAM regimen uses moxifloxacin, clofazimine, ethambutol, and pyrazinamide for nine months, supplemented by prothionamide, kanamycin, and isoniazid during an intensive phase of four months. The aim of this study is to show that this shorter treatment regimen is at least as effective as the current lengthier treatments used throughout the world to treat MDR-TB.

Looking to the pipeline, two Phase III trials are underway involving the two drugs that are close to market under conditional approval:


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- **delamanid:** A study has commenced looking at the safety and efficacy of delamanid for six months in patients with MDR-TB. It is a multicentre, randomised, double-blind, placebo-controlled, parallel group trial,[26] studying patients with culture-positive, pulmonary MDR-TB, by adding delamanid to the intensive phase of the current WHO-recommended regimen.
- **bedaquiline:** A Phase III trial comparing nine months of treatment with bedaquiline versus placebo using the background regimen of the STREAM trial is due to start recruiting patients toward the end of 2012.[27] A subpopulation of HIV co-infected patients will be included.

Other organisations are working on trials for new regimens, however the timelines for outcomes may be several years away.[28]

"TB remains the main killer of people living with HIV, and in sub-Saharan Africa we have been working to ensure people get treatment for both diseases at the same time, at the same place, and from the same health worker. For DR-TB, we've developed strategies to deliver care to people in their communities, which have shown some success. But it's extremely difficult to watch your patients try to cope with the horrendous side effects caused by this arduous two-year treatment. We urgently need treatment for DR-TB that can cure people in less time and with fewer side effects."

Dr Kazi Arif Uddin,
Matsapha Comprehensive Health Center TB Coordinator, MSF Swaziland

COMPASSIONATE USE: GETTING EXPERIMENTAL TREATMENTS TO PATIENTS WITHOUT OPTIONS

Compassionate use provides potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial. It is also called 'expanded access' or 'special access,' and became a standard approach over the years for diseases such as cancer and HIV/AIDS.

WHO approved the application of this concept to DR-TB in 2008, taking into consideration new TB compounds under clinical development.[29] For compassionate use to be implemented, a necessary regulatory framework must be in place.[29] Often in high-burden DR-TB countries, there is little experience of compassionate use and the necessary framework will need to be developed. MSF's experience in trying to secure compassionate use access to bedaquiline in South Africa shows that political will is required to ensure that this happens in a timely manner, so that patients left with few options can benefit from experimental treatments.[30]

The drug developer has the final decision on whether the drug will be supplied for compassionate use and under which conditions.

With the results of the new drugs in phase III trials and other drugs in phase II studies now published, there are a number of drugs that offer the potential for compassionate use. There needs to be greater awareness of this option to treat failing DR-TB patients, as well as the necessary regulatory framework to allow it.[31]

CONCLUSIONS AND RECOMMENDATIONS

Left untreated, drug-resistant tuberculosis kills and further encourages the disease's spread.

But with inadequate ability to diagnose DR-TB and insufficient numbers of patients on treatment, demand for DR-TB drugs is low, not least for WHO quality-assured drugs. Therefore, there is little incentive either for new producers to enter the market or for existing producers to invest in meeting WHO quality standards or increase production capacity. This creates a vicious circle, as limited drug supplies and expensive medicines in turn contribute to hindering the scale up of DR-TB treatment. Supply insecurity due to delivery delay or interruption means that programmes have been cautious rather than ambitious about the number of people they aim to treat – a direct disincentive to treatment scale-up.

Demand should be encouraged, and new diagnostic methods that allow for easier and speedier detection of DR-TB will help in this regard. However, it is crucial that access to DR-TB diagnosis is strengthened with proper implementation of current diagnostics, including Xpert MTB/RIF. This will help ensure a quicker time to diagnosis and identify the true need for DR-TB treatment.

With two new drugs active against DR-TB about to come to market, the global TB community must seize this opportunity to make a real difference in DR-TB treatment, and actively work to assess the best way of introducing the new drugs. Only a far shorter treatment regimen with far fewer side effects will be up to the task of allowing treatment providers to dramatically scale up DR-TB treatment.

The Global Drug Facility:

- Should continue to publish prices of medicines on its website in order to improve transparency
- Should work on the expansion of the existing rotating stockpile to decrease the time it takes for countries to receive medicines for all orders, and not only emergency ones
- Should further develop a strategic revolving fund with international donors to provide manufacturers a financial guarantee to secure the production and supply of second-line TB drugs

The World Health Organization:

- Should promote the use of quality-assured medicines at country level
- Should keep a balance between stimulating an optimal offer of older second-line drugs and introduction of new compounds
- Should support the evaluation of shorter treatment regimens and give timely advice on the use of new compounds

Donors:

- Should support research to define a better and shorter DR-TB treatment regimen with the inclusion of newer drugs
- Should promote the use of quality-assured medicines at country level by harmonising quality criteria for medical procurement across donors
- Should streamline supply chain mechanism both at country and global levels

Governments:

- Should commit to use medicines which meet WHO standards
- Should ensure patients have free access to a complete course of DR-TB treatment in quality programmes
- Should regulate DR-TB medicines in order to preserve their efficacy and avoid fuelling resistance
- Should establish a framework for compassionate use programmes


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"MEDICINES HAVE BECOME MY FOOD"

DR-TB treatment requires people to take a course of up to six different medicines – as many as 20 pills per day for up to two years – plus, for the first six months, a painful daily injection. Patients often endure intolerable side effects. These can include nausea, severe vomiting, depression, aggressive behaviour, hallucinations, vertigo, hearing loss, diarrhoea and lethargy. Additional medicines may be needed to mitigate these side effects.

People's lives are interrupted by DR-TB treatment, and many find adhering to it too arduous to bear. As a result, many patients abandon treatment, which increases the risk of more extensively resistant forms of the disease developing, and spreading.

Shanti,* from India, shared her story of life with DR-TB.

Shanti grew up close to the beach in Mumbai, India. In 2006, she began suffering from diarrhoea, and experienced recurring bouts of fever and vomiting. A year later, she was diagnosed with HIV and put on antiretroviral treatment.

At the same time, she was put on treatment for drug-sensitive TB, but failed to respond to all three subsequent treatment courses. Eventually, she discovered she was sick with drug-resistant TB. In 2011, she was finally able to start treatment for DR-TB through MSF.

For TB alone, Shanti had to take six tablets in the morning and eight tablets at night, in addition to her daily HIV medicines. She often said that her medicines had become her food.

The side effects of the drugs made life very difficult for Shanti.

> " I am not able to eat properly. I vomit all the time and feel drowsy the whole day long. My mind does not seem to work; I feel very distressed. I feel giddy after taking my medicine, and also unbearably hot."

By the time Shanti had come to MSF, she was very frail. She had spent much of her money getting tests that did not tell her what was wrong, and medicines that had failed to cure her – it had taken years to get the help she needed. Sadly, a few months after she started treatment with MSF, she passed away due to complications as a result of her far-gone illness.


© Bithin Das

Unfortunately, Shanti's story is far from unique. Patients who reach MSF's clinic often arrive in very bad condition and some even die before they can start their treatment. A lot of them have already been treated in the private sector with inappropriate TB drug regimens. Often, there is a lack of monitoring among private practitioners to ensure that patients take their drugs continuously. The high drug costs also force many patients in the private sector to discontinue treatment before they have been cured.

> " If the private market continues the casual over-the-counter sale of drugs, we are going to see even more cases of drug resistant TB developing" says Piero Gandini, of MSF in India. "There is an urgent need for authorities to regulate the private sector so that patients are given treatment and support of an acceptable standard."

India has the second highest MDR-TB burden in the world with nearly 66,000 new cases every year. Yet only five percent of people in India with MDR-TB are able to get the treatment they need to stay alive.[1]

> " It is really important that people with TB are correctly diagnosed at an early stage, and that appropriate care and treatment is provided. It's very sad every time we are unable to save a patient's life. But unless more is done by the authorities to address the growing problem of drug resistance, we are just going to see more cases like this" says Gandini.

* Name has been changed to protect identity

METHODOLOGY

This report looks at the sources and prices of anti-tuberculosis medicines classified Groups 2–5 in the World Health Organization's 2011 Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis, for which there are particular problems of access and for which supply is problematic or vulnerable to disruption.[32]

Grouping	Drugs
Group 1 – First-line oral agents	**isoniazid, rifampicin, ethambutol, pyrazinamide, rifabutin**
Group 2 – Injectable agents	**amikacin, kanamycin, capreomycin**
Group 3 – Fluoroquinolones	**gatifloxacin, moxifloxacin, levofloxacin, ofloxacin**
Group 4 – Oral bacteriostatic second-line agents	**ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid (PAS)**
Group 5 – Agents with unclear efficacy	**clofazimine, linezolid, amoxicillin/clavulanate, clarithromycin, imipenem, thioacetazone**

This report however does not include:

- All first-line medicines in Group 1. For first-line medicines occasionally used in DR-TB treatment, such as pyrazinamide, price is not a barrier. Attention should of course be paid to the quality of the products selected.
- Gatifloxacin in Group 3, which has not been included because of its controversial risk / benefit profile. The drug was not included in the July 2012 expression of interest of the joint Global Drug Facility / Global Fund Expert Review Panel[33] and it was not on the June 2012 WHO prequalification expression of interest list for manufacturers.[34]
- Certain medicines in Group 5, which, although listed in the WHO guidelines, are very rarely used, such as imipenem injectable, the twice-daily administration of which is complicated for both patients and treatment providers. Additional Group 5 drugs excluded are those commonly used for other indications, such as clarithromycin and amoxicillin/clavulanate, access to which is not problematic. Nevertheless, attention should be paid to these products' quality.

DATA COLLECTION

Questionnaires were sent to companies that had at least one anti-tuberculosis product either listed on the WHO List of Prequalified Medicinal Products or quality-approved by a stringent regulatory authority (SRA), according to MSF or The Union's knowledge.

The data were collected up to July 2012.

PRICE INFORMATION

Prices are listed where manufacturers agreed to share information. A number of manufacturers, including Aspen, Bayer, Mylan, Novartis, Pfizer, Teva and Vianex did not have prices available or did not agree to publish prices, and no responses were received from APP Pharma, Glenmark, and Meiji.

Prices are given in US dollars (US$), rounded up to the nearest third decimal point, and correspond to the lowest unit price (i.e. the price of one tablet, capsule or vial). When prices that varied according to packaging (e.g. blisters or bottle) were received from a manufacturer for the same formulation, the lowest price was selected. Prices received in currencies other than US$ were converted on 2 July 2012 using the currency converter site *www.oanda.com*.

Prices listed are 'ex works' except for prices provided by Cipla (FOB, Mumbai) and Macleods (FCA, Mumbai) – see annex 2 for details.

The prices listed in this publication are the ones provided by the manufacturers. The prices paid by the purchaser might be higher because of add-ons (such as import taxes and distribution mark-ups), or may be lower after negotiations or as a result of effective procurement procedures. The document should not be viewed as a manufacturers' price list.

Prices 'ex works' offered by the Global Drug Facility (GDF) pooled procurement mechanism are also listed according to the GDF catalogue available at *http://www.stoptb.org/gdf/drugsupply/drugs_available.asp* (accessed July 2012). Note that GDF prices can fluctuate during the year if, for example, a long-term agreement with different suppliers comes to an end.

QUALITY INFORMATION

Products that are either listed on the WHO List of Prequalified Medicinal Products or approved by a stringent regulatory authority are listed in the price tables as **'approved'.** Products that are undergoing review by either WHO Prequalification, by a stringent regulatory authority, or that have been reviewed and listed by the Expert Review Panel (ERP) of the Global Fund, are listed in the price tables as **'under evaluation'**.

Submissions to WHO Prequalification are confidential and all companies mentioned that have the dossier accepted for review have given MSF and The Union the permission to disclose this information. Products that have not yet been submitted to WHO Prequalification or to a stringent regulatory authority have not been included in the table.

Products procured by the Global Drug Facility comply with the GDF's Quality Assurance policy. This deems eligible for GDF procurement all products that are included on the WHO List of Prequalified Medicinal Products, that are approved by a stringent regulatory authority, or that are approved by the joint GDF / ERP. The GDF quality assurance policy can be found at: *http://www.stoptb.org/gdf/drugsupply/quality_sourcing_process.asp*

As the information on the WHO List of Prequalified Medicinal Products is updated regularly, the list should be consulted for up-to-date information, at: *http://apps.who.int/prequal/*

AMIKACIN (Am)
GROUP 2

GENERAL INFORMATION

- Therapeutic Class: Aminoglycoside antibiotic.
- ATC Code: J01GB06.[32]
- Included in the WHO Guidelines as a Group 2 injectable agent.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines[36] and in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: solution for injection: 500mg / 2ml; 100mg / 2ml. As powder for injection: 100mg, 500mg & 1g.
- First approved by US Food and Drug Administration (FDA): The date of the original New Drug Application (NDA) is not publically available on the US FDA website. The first Abbreviated New Drug Application (ANDA) was approved on 22 January 1981.[38]
- Approved indication in the US: Amikacin is indicated for the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including bacterial septicaemia (including neoatal sepsis), serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft tissue; intra-abdominal infections (including peritonitis); burns and post-operative infections (including post-vascular surgery).[39]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

AMIKACIN	Cipla	Medochemie	GDF pooled procurement price
Quality status	**WHO PQ approved**	**SRA approved / ERP approved**	**GDF Quality Assurance Policy**
500mg/2ml solution for injection	**3.250**	**0.990**	**0.962 (Medochemie)** **2.950 (Cipla)***

*This price was provided by GDF and does not appear in the online catalogue.

SPOTLIGHT ON ACCESS ISSUES

There is no clinical difference between kanamycin and amikacin. As they have similar side effect profiles and show high levels of cross-resistance,[35] factors including price, availability and adaptability of formulations will influence national TB programmes or treatment providers when selecting these drugs.

Capreomycin may be effective in cases showing resistance to amikacin.[35]

Number of quality sources

There are several stringent regulatory authority-approved sources of amikacin, however there are few sources that supply TB programmes. In January 2011, the first generic amikacin from Cipla was prequalified by WHO; Indian manufacturer Micro Labs is still expected to submit a dossier for WHO prequalification.

Manufacturer Help S.A announced that they have stopped production of amikacin.

Adaptability

Amikacin, like other aminoglycosides and capreomycin, cannot be administered orally. This imposes burdens both on treatment programmes, as qualified staff need to administer the product, and on the patient, who must undergo painful injections for eight months.

Amikacin is available in both powder and liquid formulations; the latter is more adaptable to resource-limited settings as reconstitution is not required.

Paediatrics

Amikacin is licensed for use in neonates, infants and children.[40]

There is a smaller dosage (100mg / 2ml) available which allows for more accurate dosing in children. No prices were offered for this product for this report and the product is not available through the GDF.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on pharmacokinetic profiles, the potential for drug interactions are low.

However, there is potential for additive toxicities, in particular with antiretrovirals which may cause renal toxicity, such as tenofovir.[41] Further studies are required to confirm this.

KANAMYCIN (Km)
GROUP 2

GENERAL INFORMATION

- Therapeutic Class: Aminoglycoside antibiotic.
- ATC Code: J01GB04.[32]
- Included in the WHO Guidelines as Group 2 injectable agent.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines[36] and in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: solution for injection: 1g/4ml, 500mg/2ml, 1g/3ml. As powder for injection: 1g.
- First approved by US Food and Drug Administration (FDA): The date of the original New Drug Application (NDA) is not publically available on the US FDA website. The first Abbreviated New Drug Application (ANDA) was approved on 13 February 1973. The only currently registered product in the US was approved on 17 November 2002.
- Approved indication in the US: Kanamycin is indicated in the short-term treatment of serious infections caused by susceptible strains of micro-organisms.[42]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

KANAMYCIN	Macleods	Panpharma	GDF pooled procurement price
Quality status	**Under evaluation by WHO PQ**	**SRA approved / ERP approved**	**GDF Quality Assurance Policy**
1g powder for injection	**1.510**	**0.748**	**0.790 (Panpharma)***
1g/4ml solution for injection	**xx**	**xx**	**2.580 (Meiji)**

*This price was provided by GDF and does not appear in the online catalogue.

SPOTLIGHT ON ACCESS ISSUES

There is no clinical difference between kanamycin and amikacin. As they have similar side effect profiles and show high levels of cross-resistance,[35] factors including price, availability and adaptability of formulations will influence national TB programmes or treatment providers when selecting these drugs.

Capreomycin may be effective in cases showing resistance to kanamycin.[35]

Number of quality sources

In the past, kanamycin formulations from several different manufacturers were registered in the US. However, there are currently only three kanamycin sources approved by a stringent regulatory authority: US manufacturer APP Pharma, Japan's Meiji and Panpharma in France. APP Pharma and Meiji did not respond to questionnaires for the purpose of this publication.

No sources of kanamycin are WHO-prequalified, although one manufacturer (Macleods) has submitted a dossier for WHO prequalification and has been accepted for evaluation.

The supply of kanamycin remains vulnerable, with only two sources available for TB procurement – Panpharma and Meiji – both of which have experienced production limitations. Panpharma has resolved issues with active pharmaceutical ingredient (API) production which had resulted in an interruption of supply to several national TB programmes in 2010. Meiji was identified by GDF as an alternative source in 2010; however their limited production capacity means the price of their product is considerably higher than Panpharma's.

Additional manufacturers exist in China, India, in countries from the former Soviet Union, and in other countries, but it is unknown whether they comply with WHO quality standards.

Active Pharmaceutical Ingredient

Issues with the production of the active pharmaceutical ingredient (API) have been a barrier in increasing the number of quality-assured sources for the finished product.

Kanamycin API is manufactured by a specialised process of fermentation. There are few manufacturers globally who have the capacity to produce quality-assured API through this fermentation process, and the complexity is further increased as the API should be sterile. The quality assurance of the API is a key factor in the approval of the finished product through WHO Prequalification or a stringent regulatory authority.

Adaptability

Kanamycin, like other aminoglycosides and capreomycin, cannot be administered orally. This imposes burdens both on treatment programmes, as qualified staff need to administer the product, and on patients, who must undergo painful injections for eight months.

Kanamycin is available in both powder and liquid formulations; the latter is more adaptable to resource-limited settings as reconstitution is not required.

Paediatrics

The safety and efficacy of kanamycin in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (in pharmacokinetics, pharmacodynamics, and safety data) into the use of this drug in younger populations, in particular in children aged under five.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on pharmacokinetic profiles, the potential for drug interactions are low.

However, there is potential for additive toxicities, in particular with antiretrovirals which may cause renal toxicity, such as tenofovir.[41] Further studies are required to confirm this.

CAPREOMYCIN (Cm)
GROUP 2

GENERAL INFORMATION

- Therapeutic Class: Polypeptide antibiotic.
- ATC Code: J01GB06.[32]
- Included in the WHO Guidelines as a Group 2 injectable agent.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines[36] and in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 1g powder for injection.
- First approved by US Food and Drug Administration (FDA): 2 June 1971.[43]
- Approved indication in the US: Capreomycin is used concomitantly with other appropriate anti-tuberculosis agents; it is indicated for use in pulmonary infections caused by capreomycin-susceptible strains of *M. tuberculosis* when the primary agents (isoniazid, rifampicin, ethambutol, aminosalicylic acid, and streptomycin) have been ineffective, or cannot be used because of toxicity or the presence of resistant bacilli.[43]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

CAPREOMYCIN	Akorn	Macleods	Vianex	GDF pooled procurement price
Quality status	**SRA approved / Under evaluation by WHO PQ**	**Under evaluation by WHO PQ**	**SRA approved**	**GDF Quality Assurance Policy**
1g powder for injection	**6.250**	**7.720**	**Manufacturer did not agree to publish prices**	**8.000 (Akorn)** **5.340 (Vianex)***

*This price was provided by GDF and does not appear in the online catalogue.

SPOTLIGHT ON ACCESS ISSUES

Capreomycin shows moderate cross-resistance to amikacin and kanamycin.[35]

With moxifloxacin, PAS and cycloserine, capreomycin is one of the four medicines which weigh heavily in the overall cost of a DR-TB regimen.

Number of quality sources

Eli Lilly, the original licence-holder for capreomycin, has been actively engaged in technology transfer to three generic manufacturers (Aspen, Hisun and SIA International) since 2003. However, none of these manufacturers has received approval by a stringent regulatory authority or WHO Prequalification.

GDF have identified two quality-assured sources available for supply: Akorn – which had bought Eli Lilly's US licence; and, in 2011, Vianex – a manufacturer based in Greece, which has received stringent regulatory authority approval in Spain.

With only two quality-assured sources currently available for TB procurement, the supply of capreomycin is still considered vulnerable; however, three companies, including Macleods and Aspen, have submitted a dossier for WHO prequalification.

Active Pharmaceutical Ingredient

Issues with the production of the active pharmaceutical ingredient (API) have been a barrier in increasing the number of quality-assured sources for the finished product.

Capreomycin API is manufactured by a specialised process of fermentation. There are few manufacturers globally who have the capacity to produce quality-assured API through this fermentation process, and the complexity is further increased as the API should be sterile. The quality assurance of the API is a key factor in the approval of the finished product through WHO Prequalification or a stringent regulatory authority.

Eli Lilly transferred the technology for capreomycin API to only one manufacturer, Chinese generic producer Hisun, which received US FDA approval in 2006.

Other API manufacturers exist, but have not been approved by a stringent regulatory authority or by the WHO Prequalification Programme.

Evolution in price

For a number of years, Eli Lilly subsidised the price of capreomycin for GLC-approved programmes, charging US$1.02 per vial until a certain volume had been ordered, and $4.00 thereafter.

Since transferring the technology to other manufacturers, however, the price at which countries can procure capreomycin has increased considerably. With Eli Lilly's stock now exhausted, the subsidised price of $4.00 per vial is no longer available. GDF procures the Akorn product at a price of $8.00 per vial, although the company provided a price of $6.25 per vial to this publication. Vianex-sourced capreomycin is available for GDF procurement at $5.34 per vial.

However, with a new quality-assured source identified and three suppliers set to receive WHO prequalification, it is anticipated the price will eventually decrease.

Adaptability

Capreomycin, like DR-TB medicines from the aminoglycosides class, cannot be administered orally. This imposes burdens both on treatment programmes, as qualified staff need to administer the product, and on patients, who must undergo painful injections for eight months.

Paediatrics

The safety and efficacy of capreomycin in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on pharmacokinetic profiles, the potential for drug interactions are low.

However, there is potential for additive toxicities, in particular with antiretrovirals which may cause renal toxicity such as tenofovir.[41] Further studies are required to confirm this.

MOXIFLOXACIN (Mfx)
GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone.
- ATC Code: J01MA14.[32]
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.[35]
- Not included in the 17th edition of the WHO Model List of Essential Medicines[36] nor in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 400mg tablet.
- First approved by US Food and Drug Administration (FDA): 12 October 1999.[44]
- Approved indication in the US: Moxifloxacin was initially approved for the indications of bacterial sinusitis and community-acquired pneumonia. This was further expanded to include acute bacterial exacerbation of chronic bronchitis, uncomplicated and complicated skin and skin structure infection, and complicated intra-abdominal infections.[45]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

MOXIFLOXACIN	Bayer	Cipla	Hetero	Macleods	GDF pooled procurement price
Quality status	**SRA approved**	**WHO PQ approved**	**Under evaluation by WHO PQ**	**Under evaluation by WHO PQ**	**GDF Quality Assurance Policy**
400mg tab	**Manufacturer did not agree to publish prices**	**1.850**	**1.100**	**1.600**	**1.680 (Cipla)** **1.500 (Macleods)***

*This price was provided by GDF and does not appear in the online catalogue.

SPOTLIGHT ON ACCESS ISSUES

Based on 2011 WHO DR-TB programmatic guidelines, the use of later generation fluoroquinolones, such as moxifloxacin and levofloxacin, are preferred to ofloxacin.[35]

With capreomycin, PAS and cyloserine, moxifloxacin is one of the four medicines which weigh heavily in the overal cost of a DR-TB regimen.

Number of quality sources

Bayer was the only quality-assured source of moxifloxacin available for many years. In November 2010, Cipla's product became the first generic moxifloxacin to be prequalified by WHO and a second manufacturer (Macleods) has since submitted a dossier that has been accepted for evaluation.

Meanwhile, the Macleods product received joint GDF/Global Fund Expert Review Panel approval in June 2012, making it eligible for procurement for Global Fund grants.

Further sources of quality-assured moxifloxacin are also expected as other approved indications of use exist for the drug. There are currently three generic manufacturers (Dr Reddy's, Teva, Torrent Pharms) that have tentative US FDA approval, waiting to enter the US market when the patent expires in 2019.

Although price remains a barrier, the supply of moxifloxacin will therefore be relatively secure in the near future.

Additional manufacturers exist in China, India, in countries from the former Soviet Union, and in other countries, but it is unknown whether they comply with WHO quality standards.

Evolution in price

After the arrival of a quality-assured generic onto the market, the price has reduced considerably. Prior to this, the only option available was Bayer; prices for this product reported in the Global Fund Price and Quality Reporting (PQR) tool have ranged between US$3.97 and $5.03 per tablet in the last four years.[46]

Cipla provided a quality-assured FOB price of $1.85 per tablet; GDF reports an ex works price of $1.68 for the same product. As more generic manufacturers enter the market, it is expected the price will fall further.

Approved indication

While moxifloxacin has been shown to be effective against *M. tuberculosis*, it has not yet received an approved TB indication by any stringent regulatory authority.

Patents

Although the basic patent which covered the moxifloxacin molecule has now expired in most countries,[47] a subsequent patent claiming a crystal monohydrate form of moxifloxacin[48] was filed which blocks generic production in countries where the patent is granted. An addition, a patent on the tablet oral formulation[49] appears to stand in the way of generic production in the US market until 2019 (see box on US patents).

The following patents are listed by the US FDA for moxifloxacin 400mg tablet:[50]

US patent number.	Expiry date
4990517	8 December 2011
5607942	4 March 2014
5849752	5 December 2016
6610327	29 October 2019

In India, where the patent on the crystal monohydrate form was rejected after a pre-grant opposition, additional patents on other pharmaceutical forms have been granted, but these do not block generic manufacturing of the tablet formulation.

Similarly, generic versions have now been registered in South Africa and are supplied for DR-TB treatment through the National TB programme as part of the government tender awarded in 2011. Generic versions are also marketed in the Russian Federation.

Paediatrics

The safety and efficacy of moxifloxacin in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on the metabolism rate of moxifloxacin, levels of the drug may be reduced by use of ritonavir and increased by atazanavir. Further research is needed to assess this.

Protease inhibitors and efavirenz may prolong QT interval, so caution is advised in concomitant use with moxifloxacin, with electrocardiogram monitoring recommended.

Oral absorption of fluoroquinolones is reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets.[41]

LEVOFLOXACIN (Lfx)
GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone.
- ATC Code: J01MA12.[32]
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines[36] and in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37] Levofloxacin is considered a better alternative to ofloxacin, based on availability and programme considerations.
- Presentations available: 250mg, 500mg and 750mg tablets; 25mg/ml oral solution.
- First approved by US Food and Drug Administration (FDA): 20 December 1996. The paediatric formulation (25mg/ml oral solution) was approved on 21 October 2004.[51]
- Approved indication in the US: Levofloxacin was initially approved for the indications of acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, uncomplicated skin and skin structure infections, complicated urinary tract infections (UTI), and acute pyelonephritis. This was further expanded to include uncomplicated UTI, chronic bacterial prostatitis, and treatment of inhalational anthrax (post-exposure).[51]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

LEVOFLOXACIN	Cipla	Hetero	Macleods	Micro Labs	GDF pooled procurement price
Quality status	**SRA approved / WHO PQ approved**	**Under evaluation by WHO PQ / Under evaluation by SRA / ERP approved**	**Under evaluation by WHO PQ**	**WHO PQ approved**	**GDF Quality Assurance Policy**
250mg tab	**0.061**	**0.060**	**0.060**	**0.090**	**0.050 (Cipla)**
500mg tab	**0.085**	**0.092**	**0.075**	**0.160**	**0.080 (Cipla)**
750mg tab	**Manufacturer did not agree to publish prices**	**xx**	**xx**	**xx**	**xx**

SPOTLIGHT ON ACCESS ISSUES

Based on 2011 WHO DR-TB programmatic guidelines, the use of later generation fluoroquinolones, such as moxifloxacin and levofloxacin, are preferred to ofloxacin.[35]

Number of quality sources

Levofloxacin 250mg and 500mg oral formulations produced by Micro Labs and Cipla are prequalified by WHO. Hetero (250mg and 500mg) and Macleods have submitted their dossiers for WHO prequalification. In addition, Hetero has received joint GDF/Global Fund Expert Review Panel approval, making their 250mg and 500mg products eligible for Global Fund procurement.

With patents in the US having expired in June 2011, there are currently 13 manufacturers that have 250mg, 500mg or 750mg formulations registered with the US FDA. These manufacturers could be potential suppliers to GDF and national TB programmes in the future.

The price of levofloxacin does not appear to be an issue.

Approved indication

The 2011 WHO programmatic guidelines for DR-TB recommend use of later generation fluorquinolones, including levofloxacin. However, levofloxacin does not have a TB indication approved by any stringent regulatory authority.[35]

Patents

Patents in the US and in several European countries claiming levofloxacin expired in June 2011.

Paediatrics

The US FDA has approved levofloxacin for use in children aged over six months, but only for acute infections. The safety of levofloxacin in children treated for more than 14 days has not been studied; as this drug may be taken for up to two years, there is an urgent need for more safety data on the use of levofloxacin for extended periods of time in children.

While there are two manufacturers of the paediatric formulation (25mg/ml oral solution) available in the US, these are not widely available elsewhere. Currently, the majority of DR-TB programmes prepare paediatric doses by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent. Paediatric formulations need to be made more widely available.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on the metabolism rate of levofloxacin, no interactions are expected. However, further research is needed to assess this.

Protease inhibitors and efavirenz may prolong QT interval, so caution is advised in concomitant use with levofloxacin, with electrocardiogram monitoring recommended.

Oral absorption of fluoroquinolones is reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets.[41]

OFLOXACIN (Ofx)
GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone.
- ATC Code: JJ01MA01.[32]
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines[36] and in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 200mg, 300mg, 400mg tablet.
- First approved by US Food and Drug Administration (FDA): 28 December 1990.[44]
- Approved indication in the US: Ofloxacin is approved for the indications of acute bacterial exacerbations of chronic bronchitis, acute uncomplicated uretheral and cervical gonorrhea, non-gonococcal urethritis and cervicitis, acute pelvic inflammatory disease, and uncomplicated skin and skin structure infections.[52]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

OFLOXACIN	Cipla	Macleods	Medochemie	Micro Labs	GDF pooled procurement price
Quality status	**WHO PQ approved**	**WHO PQ approved**	**SRA approved / ERP approved**	**WHO PQ approved**	**GDF Quality Assurance Policy**
200mg tab	**0.055**	**0.060**	**0.095**	**0.060**	**0.050 (Cipla)**
400mg tab	**0.099**	**xx**	**xx**	**0.110**	**0.090 (Cipla)**

SPOTLIGHT ON ACCESS ISSUES

Based on 2011 WHO DR-TB programmatic guidelines, the use of later generation fluoroquinolones, such as moxifloxacin and levofloxacin, are preferred to ofloxacin.[35]

Number of quality sources

Ofloxacin formulations produced by Cipla, Macleods and Micro Labs have received WHO prequalification. Micro Labs has also received joint GDF / Global Fund Expert Review Panel approval, making it eligible for Global Fund procurement.

As the patent for ofloxacin has expired, other generic manufacturers (including Teva and Dr. Reddy's) have now entered the market, with products available in the US and Europe.

Approved indication

The 2011 WHO DR-TB programmatic guidelines recommend use of later generation fluoroquinolones. As with other Group 3 drugs, ofloxacin does not have a TB indication approved by any stringent regulatory authority.

Paediatrics

The safety and efficacy of ofloxacin in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent.

HIV co-infection

No antiretroviral interaction studies have been performed, however one source suggests there may be potential interactions with atazanavir and lopinavir.[53]

Protease inhibitors and efavirenz may prolong QT interval, so caution is advised in concomitant use with ofloxacin, with electrocardiogram monitoring recommended.

Oral absorption of fluoroquinolones is reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets.[41]

ETHIONAMIDE (Eto)
GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Carbothionamides group, derivative of isonicotinic acid.[35]
- ATC Code: J04AD03.[32]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines[36] and in 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 250mg tablet.
- First approved by US Food and Drug Administration (FDA): 30 April 1965.[44]
- Approved indication in the US: ethionamide is primarily indicated for the treatment of active tuberculosis in patients with *M. tuberculosis* resistant to isoniazid or rifampicin, or where the patient is intolerant to other drugs.[54]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

ETHIONAMIDE	Cipla	Lupin	Macleods	Micro Labs	Pfizer	GDF pooled procurement price
Quality status	**WHO PQ approved**	**Under evaluation by WHO PQ / ERP approved**	**WHO PQ approved**	**Under evaluation by WHO PQ**	**SRA approved**	**GDF Quality Assurance Policy**
250mg tab	**0.091**	**Manufacturer did not agree to publish prices**	**0.095**	**0.078**	**Manufacturer did not agree to publish prices**	**0.080 (Cipla) 0.073 (Macleods)* 0.079 (Lupin)***

*This price was provided by GDF and does not appear in the online catalogue.

SPOTLIGHT ON ACCESS ISSUES

Prothionamide is the propyl analog of ethionamide. There is complete cross-resistance between the two drugs and they are used interchangeably.[55]

Number of quality sources

As of December 2011, there were three quality-assured sources of ethionamide, with Cipla 250mg tablets having received WHO prequalification; Macleods and Wyeth Pharm – under licence from Pfizer – also produce quality-assured products.

In addition, Lupin and Micro Labs have submitted their dossiers for WHO prequalification, while Lupin has also received joint GDF/ Global Fund Expert Review Panel approval, making it eligible for Global Fund procurement.

With an additional quality-assured source now approved and more are expected in the future, the supply and number of sources of ethionamide is gradually improving.

The price of ethionamide does not appear to be an issue.

Paediatrics

The safety and efficacy of ethionamide in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent.

HIV co-infection

While no antiretroviral interaction studies have been performed, pharmacokinetic profiles suggest that drug interactions with ethionamide are possible.

There is the possibility of additive toxicities with antiretrovirals which may cause hepatotoxicity, including efavirenz and nevirapine.[41]

With the potential for interactions with some classes of antiretrovirals, there is an urgent need for further studies.

PROTHIONAMIDE (Pto)
GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Carbothionamides group, derivative of isonicotinic acid.[35]
- ATC Code: J04AD01.[32]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.[35]
- Not included in the 17th edition of the WHO Model List of Essential Medicines[36] nor in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 250mg tablet.
- First approved by German Federal Institute for Drugs and Medical Devices (BfArM): First marketed in Germany in the 1970s but registered in the framework of posterior registration process in Germany on 14 June 2005.[56]
- Approved indication in Germany: Treatment of all forms and stages of pulmonary and extra-pulmonary tuberculosis as second-line drug in the case of proven multidrug-resistance of the pathogens against first-line drugs; treatment of diseases caused by so-called ubiquitous (atypical) mycobacteria; treatment of leprosy in the context of modified therapy regimens.[57]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

PROTHIONAMIDE	Fatol	Lupin	Micro Labs	Olainfarm	GDF pooled procurement price
Quality status	**SRA approved**	**Under evaluation by WHO PQ / ERP approved**	**Under evaluation by WHO PQ / ERP approved**	**SRA approved**	**GDF Quality Assurance Policy**
250mg tab	**0.126**	**Manufacturer did not agree to publish prices**	**0.080**	**0.140**	**0.127 (blister) (Fatol) 0.080 (bottle) (Lupin)**

SPOTLIGHT ON ACCESS ISSUES

Prothionamide is the propyl analog of ethionamide. There is complete cross-resistance between the two drugs and they are used interchangeably.[55]

Number of quality sources

Only two sources of prothionamide have received stringent regulatory authority approval (Germany's Fatol and Latvia's Olainfarm), while none have been WHO-prequalified. However, Lupin and Micro Labs have submitted their dossiers for WHO prequalification.

Lupin and Micro Labs have also received joint GDF/Global Fund Expert Review Panel approval, making them eligible for Global Fund procurement, while Olainfarm is likewise considered eligible for procurement under the Global Fund quality assurance policy.

The increasing number of quality-assured sources of prothionamide is gradually improving its supply, and the price of prothionamide is expected to fall further.

Paediatrics

The safety and effectiveness of prothionamide in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent.

HIV co-infection

While no antiretroviral interaction studies have been performed, pharmacokinetic profiles suggest that drug interactions with prothionamide are possible.

There is the possibility of additive toxicities with antiretrovirals which may cause hepatotoxicity, including efavirenz and nevirapine.[41]

With the potential for interactions with some classes of antiretrovirals, there is an urgent need for further studies.

CYCLOSERINE (Cs)
GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Analog of D-alanine.[35]
- ATC Code: J04AB01.[32]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines[36] and in 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 250mg capsule.
- First approved by US Food and Drug Administration (FDA): 29 June 1964.[44]
- Approved indication in the US: Cycloserine is indicated in the treatment of active pulmonary and extra-pulmonary tuberculosis (including renal disease), when the causative organisms are susceptible to this drug and when treatment with the primary medications (streptomycin, isoniazid, rifampicin and ethambutol) has proved inadequate.[58]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

CYCLOSERINE	Aspen	Chao Center / Purdue	Lupin	Macleods	GDF pooled procurement price
Quality status	**WHO PQ approved**	**SRA approved**	**Under evaluation by WHO PQ / ERP approved**	**WHO PQ approved**	**GDF Quality Assurance Policy**
250mg cap	**Manufacturer did not agree to publish prices**	**0.580**	**Manufacturer did not agree to publish prices**	**0.593**	**0.580 (blister) (Macleods) 0.780 (bottle 100) (Aspen) 0.800 (bottle 40) (Chao Center)**

Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

With capreomycin, moxifloxacin, and PAS, cycloserine is one of the four medicines which weigh heavily in the overall cost of a DR-TB regimen.

Number of quality sources

Eli Lilly, the original licence holder of cycloserine, has actively engaged in technology transfer to three generic manufacturers (Aspen, Chao Center/ Purdue GMP and SIA International) and ceased production in 2008.

There are currently three quality-assured sources of cycloserine, with Macleods and Aspen sources now WHO-prequalified, and Chao Center/ Purdue having stringent regulatory authority approval.

Four other manufacturers, including Lupin and Cipla, have submitted dossiers for WHO prequalification, meaning the supply of quality-assured cycloserine is relatively secure.

Active Pharmaceutical Ingredient

Until 2006, the only quality-assured source for the active pharmaceutical ingredient of cycloserine was Eli Lilly. The company completed a technology transfer for the API to Indian manufacturer Shasun, in 2006. Shasun API was subsequently US FDA approved in June 2008.

Evolution in price

Since 2001, the GDF-sourced price of cycloserine has risen, from an Eli Lilly-subsidised price of US$0.14 per capsule to $0.58 per capsule in the wake of technology transfers.[59]

With a number of quality-assured sources, and more expected in the future, the price of cycloserine is expected to fall with increased competition.

Paediatrics

The British National Formulary provides doses for children aged two to 18, while the US FDA states that the safety and effectiveness of cycloserine in children has not been established.

There is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent.

HIV co-infection

The metabolism of cycloserine is not completely understood, and therefore interactions with antiretrovirals are unpredictable.[41]

There is a need for more research into potential interactions between antiretrovirals and cycloserine.

TERIZIDONE (Trd)
GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Analog of D-alanine.[35]
- ATC Code: J04AK03.[32]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.[35]
- Not included in the 17th edition of the WHO Model List of Essential Medicines[36] nor in 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 250mg capsule.
- First approved by German Federal Institute for Drugs and Medical Devices (BfArM): First marketed in Germany in the 1970s and is still in the process of the posterior registration process in Germany. The filing date for this process was 1 January 1978.[56]
- Approved indication in Germany: Treatment of tuberculosis in adults and adolescents aged 14 or older.[56]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

TERIZIDONE	Fatol	GDF pooled procurement price
Quality status	**SRA approved**	**GDF Quality Assurance Policy**
250mg cap	**1.489**	**1.494 (Fatol)**

SPOTLIGHT ON ACCESS ISSUES

Terizidone is a combination of two molecules of cycloserine, and as such has a similar mode of action as cycloserine. There is complete cross-resistance to cycloserine,[57] and, in some countries, the drug is used instead of cycloserine.

Number of quality sources

Germany's Fatol is currently the sole quality-assured source of terizidone. Currently no manufacturers have submitted dossiers for WHO prequalification.

Additional manufacturers exist, but it is unknown whether they comply with WHO quality standards.

Paediatrics

The safety and effectiveness of terizidone in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent.

HIV co-infection

As terizidone is a combination of two molecules of cycloserine and the metabolism of cycloserine is not completely understood, interactions with antiretrovirals are unpredictable.[41]

There is a need for more research into potential interactions between antiretrovirals and terizidone.

PARA-AMINOSALICYLIC ACID (PAS) AND PARA-AMINOSALICYLATE SODIUM (PAS-Sodium)
GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Salicylic acid anti-folate.[35]
- ATC Code: for PAS: J04AA01; for PAS-Sodium: J04AA02.[32]
- Included in the WHO Guidelines: PAS: as a Group 4 oral bacteriostatic second-line agent; PAS-Sodium: not included.[35]
- PAS is included in the 17th edition of the WHO Model List of Essential Medicines[36] and in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37] PAS-Sodium is not included in either document.
- Presentations available: PAS: 4g sachet. PAS-Sodium: 60% weight for weight granules 9.2g sachet and 100g jar; powder for solution 5.52g sachet (equivalent to PAS 4g sachet).
- First approved by US Food and Drug Administration (FDA): PAS-Sodium was first registered in a tablet formulation on 8 March 1950. Currently, only PAS is available in the US, with the product registered on 30 June 1994.[60]
- Approved indication in the US: PAS is indicated for the treatment of tuberculosis in combination with other active agents. It is most commonly used in patients with multidrug-resistant TB or in situations when therapy with isoniazid and rifampicin is not possible due to a combination of resistance and/or intolerance.[60]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

PAS	Jacobus	GDF pooled procurement price
Quality status	**SRA approved**	**GDF Quality Assurance Policy**
4g sachet	**1.567**	**1.530 (Jacobus)**

PAS-SODIUM	Macleods	Olainfarm	GDF pooled procurement price
Quality status	**WHO PQ approved**	**SRA approved**	**GDF Quality Assurance Policy**
60% w/w granules – 9.2g sachet	**1.510**	**xx**	**1.450 (Macleods)**
60% w/w granules – 100g jar	**16.270 (1.497 for 9.2g)**	**xx**	**16.000 (Macleods) (1.472 for 9.2g)**
Powder for solution – 5.25g sachet	**xx**	**1.550**	**1.500 (Olainfarm)**

SPOTLIGHT ON ACCESS ISSUES

Para-aminosalicylate sodium (PAS-Sodium) is the sodium salt of para-aminosalicylic acid (PAS), with 1.38g of PAS-Sodium equivalent to approximately 1g of PAS.[61]

With none of the quality-assured sources of either PAS or PAS-Sodium presented in the same formulation – the concentration of PAS varies between product and manufacturer[61] – dosing can be can be particularly confusing if multiple formulations exist in one treatment programme.

With moxifloxacin, capreomycin and cycloserine, PAS is one of the four medicines which weigh heavily in the overall cost of a DR-TB regimen.

Number of quality sources

There is currently only one quality-assured source of PAS (Jacobus), and just two quality-assured sources of PAS-Sodium (Macleods and Olainfarm), with no other sources in the pipeline.

The Macleods PAS-Sodium received WHO prequalification in 2009, but the unexpectedly large demand for this product led to capacity problems, resulting in long lead times for orders. This was resolved in 2011.

With three quality-assured sources of PAS and PAS-Sodium now available for procurement, supply has improved, but is still considered vulnerable, particularly as the different formulations available are not easily interchangeable.

Adaptability

The various formulations have different storage conditions, which can present issues for treatment programmes.

While PAS-Sodium products do not require any special storage conditions, PAS is required to be stored in a cold chain below 15°C. This is problematic for many settings where DR-TB is prevalent, as maintaining a functional cold chain requires a certain level of investment both in infrastructure and human resources.

However, the latest PAS stability data states that PAS can be kept in conditions below 40°C and 75% humidity for one month without risk of degradation, if required.

Paediatrics

The safety and effectiveness of PAS and PAS-Sodium in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations. With all adult formulations varying in strength and in either granule or powder presentations, measuring the exact dose for a child is difficult and requires calibrated scales to be available at the point of dispensing.

Some manufacturers are now supplying a graduated dosage scoop for PAS which allows for a more accurate paediatric dosage, or measuring spoons for PAS-Sodium, but these methods are still not completely accurate.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on the pharmacokinetic profile of PAS, drug interactions are unlikely. Studies should be performed to confirm this.[41]

CLOFAZIMINE (Cfz)
GROUP 5

GENERAL INFORMATION

- Therapeutic Class: Phenazine Derivative.[35]
- ATC Code: J04BA01.[32]
- Included in the WHO Guidelines as a Group 5 medicine; agents with unclear efficacy.[35]
- Included in the 17th edition of the WHO Model List of Essential Medicines (as an anti-leprosy medicine)[36] and in the 3rd edition of the WHO Model List of Essential Medicines for Children (as an anti-leprosy medicine).[37]
- Presentations available: 50mg and 100mg soft-gel capsules.
- First approved by US Food and Drug Administration (FDA): 15 December 1986.[62]
- Approved indication in US: Clofazimine is indicated in the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum.[62]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

Clofazimine is a Group 5 medicine which is used in patients with XDR-TB, currently a very small market. This medicine does not exist in the GDF product catalogue.

CLOFAZIMINE	Novartis	GDF pooled procurement price
Quality status	**SRA approved**	**xx**
50mg soft-gel cap	**Manufacturer did not agree to publish prices**	**xx**

SPOTLIGHT ON ACCESS ISSUES

Clofazimine was first synthesised in 1954 as an anti-TB compound, but was subsequently thought to be ineffective against TB. In 1959, clofazimine demonstrated effectiveness against leprosy and, after clinical trials, was launched by Novartis for use in leprosy in 1969.

In late 1999, Novartis signed a Memorandum of Understanding with the WHO leprosy programme for a donation of clofazimine. In the past few years, the GLC and the GDF were able to source small quantities of clofazimine through the Leprosy Program at WHO – which procures the medicine through Novartis – and supply a few countries. As the programmes' demand for this drug increased, this supply channel could no longer support the volumes needed by MDR-TB projects. Together with GLC partners, the GDF therefore approached Novartis in an attempt to secure clofazimine, but so far no agreement has been reached.[63]

Clofazimine has no official indication for the treatment of DR-TB, and as its effectiveness has not been established, it is not routinely used for DR-TB treatment. The 2011 WHO programmatic guidelines recommend the use of clofazimine for patients with MDR/XDR-TB, when there are no other options available. A systematic review published in October 2012 suggests that clofazimine could be considered as an additional therapeutic option in the treatment of DR-TB.[64]

Novartis does not make this drug available for DR-TB treatment on the basis of a lack of efficacy and safety data, and owing to concerns over liability for off-label use. For these reasons, Novartis chose not submit a price for this publication.

WHO is currently in discussion with Novartis to address the liability for off-label use and patient safety of clofazimine for TB use, and hopes to have the drug available for MDR and XDR-TB treatment as soon as possible.[2]

Number of quality sources

Clofazimine produced by Sandoz for Novartis is currently the sole quality-assured source of the drug. Additional manufacturers exist in India and Europe, but it is unknown whether they comply with WHO quality standards. With no market for clofazimine in developed countries, there is no reason for manufacturers to seek stringent regulatory authority approval.

In order to send a clear message to manufacturers that clofazimine is needed, a call to include the drug in the WHO Prequalification Expression of Interest (EoI) was issued. However, in June 2012, the drug was not included in the 11th Invitation to Manufacturers to submit expressions of interest for WHO prequalification. Meanwhile, clofazimine continues to be included in the joint GDF/Global Fund Invitation to Manufacturers to submit an Expression of Interest for product evaluation issued by the Expert Review Panel.

As demand for clofazimine is expected to increase, there is a need for alternative sources of the drug other than the existing Novartis product, which is not easily available.

For patients who require this drug, it can be purchased through certain private pharmacies. The GDF catalogue does not list clofazimine, but it can be procured at a price of US$1.12 per 100mg capsule through a supplier in Switzerland.[65]

Paediatrics

The safety and effectiveness of clofazimine in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five.

A 50mg soft-gel capsule is currently available, but this formulation makes it impossible to fraction the dose. This puts clinicians in a difficult position, with risks of either over-dosing the child and increasing the risk of side effects, or under-dosing and increasing the risk of amplification of the child's resistance profile.

HIV co-infection

Clofazimine may have a significant drug-drug interaction with some antiretrovirals. No studies have been performed, but clofazimine is a weak inhibitor of the CYP3A4 metabolism pathway and may increase levels of protease inhibitors and etravirine.[41]

LINEZOLID (Lzd)
GROUP 5

GENERAL INFORMATION

- Therapeutic Class: Oxazolidinone antibiotic.
- ATC Code: J01XX08.[32]
- Included in the WHO Guidelines as a Group 5 medicine; agents with unclear efficacy.[35]
- Not included in the 17th edition of the WHO Model List of Essential Medicines[36] nor in the 3rd edition of the WHO Model List of Essential Medicines for Children.[37]
- Presentations available: 600mg tablet, 100mg / 5ml powder for suspension.
- First approved by US Food and Drug Administration (FDA): 18 April 2000.[66]
- Approved indication in US: Linezolid is indicated for treatment of susceptible strains of designated microorganisms for nosocomial pneumonia; and complicated and uncomplicated skin and skin structure infections. It is not indicated for the treatment of Gram-negative infections and community-acquired pneumonia.[67]

PRICE (IN US$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

Linezolid is a Group 5 medicine which is used in patients with XDR-TB, currently a very small market. This medicine does not exist in the GDF product catalogue.

LINEZOLID	Hetero	Pfizer	GDF pooled procurement price
Quality status	**Under evaluation by SRA**	**SRA approved**	**xx**
600mg tab	**2.500**	**Manufacturer did not agree to publish prices**	**xx**
100mg/ml powder for susp.	**xx**	**Manufacturer did not agree to publish prices**	**xx**

SPOTLIGHT ON ACCESS ISSUES

Although linezolid has no official indications for DR-TB treatment, clinical data on use in TB has been published. The 2011 WHO programmatic guidelines recommend the use of linezolid for patients with MDR or XDR-TB. In April 2012, a systematic review outlined the efficacy of linezolid in DR-TB treatment.[68]

Linezolid has a relatively high number of adverse side effects, including myelosuppression, anaemia, and irreversible peripheral and optical neuropathies. Nonetheless, linezolid plays an important role in patients with XDR-TB.

Number of quality sources

Currently, only one manufacturer – Pfizer – is approved by a stringent regulatory authority.

A further four manufacturers (Teva, Mylan, Glenmark and Gate Pharma) have tentative approval from the US FDA; however, there appears to be no willingness to produce linezolid and supply the DR-TB market with quality-assured drugs before the patents expire in 2021.

Despite the call for linezolid to be included in the WHO Prequalification Expression of Interest for product evaluation, the drug was not included in the 11th Invitation to Manufacturers issued in July 2012. However, linezolid is included in the joint GDF / Global Fund Invitation to Manufacturers to submit an Expression of Interest for product evaluation issued by the Expert Review Panel (ERP).

Macleods subsequently submitted a dossier for evaluation to the ERP. Indian generic manufacturer Hetero has also submitted a dossier for linezolid to the US FDA.

Additional manufacturers exist in India, but it is unknown whether they comply with WHO quality standards.

Evolution in price

No price was supplied for linezolid from GDF for this publication, and there are no entries in the Global Fund Price and Quality Reporting (PQR) tool.

Due to patents covering linezolid in the US and a number of other countries, the cost of the drug is extremely high. For example, the price of Pfizer-produced linezolid in the South African private sector is US$81.00 per tablet[63]. At this price, the cost of linezolid alone for one patient is nearly $60,000 for two years' treatment. Patients failing conventional DR-TB treatments but who could have a chance to survive through the use of linezolid, are denied this option due to the prohibitively expensive cost.

The search for more alternative quality-assured sources is critical to ensure price reductions.

Patents

The basic patent claiming linezolid was filed by Upjohn Company in the US in 1993 and will expire on 18 November 2014.[70] Upjohn Company also filed patents in the US on a crystalline form[71] and on a tablet formulation in 2002;[72] these patents will impede generic competition in the US until 2021.

The following patents are listed by the US FDA for linezolid:[50]

US patent number.	Expiry date
5688792	18 November 2014
6514529	15 March 2021
6559305	29 January 2021
6610327	29 October 2019

The patents claiming crystal forms and the tablet formulation have also been granted in many developing countries including Argentina, Brazil, China, Colombia, Mexico, Ukraine and South Africa. These patents could also impede the introduction of generic versions.

In India the basic compound patent could not be filed as in 1993, the local patent law did not allow pharmaceutical product patenting. The generic version is now available in India.

Paediatrics

Pharmacokinetic studies have been completed in children from birth, and dosages are approved by the US FDA exclusively for infections with gram-positive bacteria resistant to other antibiotics.

A paediatric formulation exists as a powder for suspension, produced by Pfizer. The reconstituted product can be stored at room temperature.

There is a need for further safety and efficacy data on the use of linezolid for extended periods in children with DR-TB.

HIV co-infection

No antiretroviral interaction studies have been performed but interactions are unlikely. There may, however, be an increased risk of myelosuppression and mitochondrial toxicities with long-term use in combination with certain antiretrovirals (zidovudine, stavudine, didanosine).[41] Further studies are required to confirm this.

ANNEX 1: SUMMARY TABLE OF PRICES PROVIDED BY PHARMACEUTICAL COMPANIES

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

Products included in the WHO List of Prequalified Medicinal Products and/or approved by a stringent regulatory authority (SRA) are in **bold**.

Products that are under evaluation by WHO prequalification and/or SRAs, and/or approved by ERP are underlined.

Prices listed with a * were provided directly by GDF and do not appear in the GDF online catalogue.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

Drug	GDF pooled procurement price	Companies				
AMIKACIN	**GDF**	**Cipla**	**Medochemie**			
500mg/2ml solution for injection	0.962 (Medochemie) 2.950 (Cipla)*	**3.250**	**0.990**			
KANAMYCIN		**Macleods**	**Panpharma**			
1g powder for injection	0.790 (Panpharma)*	1.510	**0. 748**			
1g/4ml solution for injection	2.580 (Meiji)					
CAPREOMYCIN		**Akorn**	**Macleods**	**Vianex**		
1g powder for injection	8.000 (Akorn) 5.340 (Vianex)*	**6.250**	**7.720**	**Manufacturer did not agree to publish prices**		
MOXIFLOXACIN		**Bayer**	**Cipla**	**Hetero**	**Macleods**	
400mg tablet	1.680 (Cipla) 1.500 (Macleods)*	**Manufacturer did not agree to publish prices**	**1.850**	1.100	1.600	
LEVOFLOXACIN		**Cipla**	**Hetero**	**Macleods**	**Micro Labs**	
250mg tablet	0.050 (Cipla)	**0.061**	0.060	0.060	**0.090**	
500mg tablet	0.080 (Cipla)	**0.085**	0.092	0.075	**0.160**	
750mg tablet		**Manufacturer did not agree to publish prices**				
OFLOXACIN		**Cipla**	**Macleods**	**Medochemie**	**Micro Labs**	
200mg tablet	0.050 (Cipla)	**0.055**	**0.060**	**0.095**	**0.060**	
400mg tablet	0.090 (Cipla)	**0.099**			**0.110**	
ETHIONAMIDE		**Cipla**	**Lupin**	**Macleods**	**Micro Labs**	**Pfizer**
250mg tablet	0.080 (Cipla) 0.073 (Macleods)* 0.079 (Lupin)*	**0.091**	Manufacturer did not agree to publish prices	**0.095**	0.078	**Manufacturer did not agree to publish prices**
PROTHIONAMIDE		**Fatol**	**Lupin**	**Micro Labs**	**Olainfarm**	
250mg tablet	0.127 (blister) (Fatol) 0.080 (bottle) (Lupin)	**0.126**	Manufacturer did not agree to publish prices	0.080	**0.140**	

Drug	GDF pooled procurement price	Companies				
CYCLOSERINE	**GDF**	**Aspen**	**Chao Centre/ Purdue**	**Lupin**	**Macleods**	
250mg capsule	0.580 (blister) (Macleods) 0.780 (bottle 100) (Aspen) 0.800 (bottle 40) (Chao Center/ Purdue)	**Manufacturer did not agree to publish prices**	**0.580**	Manufacturer did not agree to publish prices	**0.593**	
TERIZIDONE		**Fatol**				
250mg capsule	1.494 (Fatol)	**1.489**				
PAS		**Jacobus**				
4g sachet	1.530 (Jacobus)	**1.567**				
PAS-SODIUM		**Macleods**	**Olainfarm**			
60% w/w granules – 9.2g sachet	1.450 (Macleods)	**1.510**				
60% w/w granules – 100g jar	16.000 (1.472 for 9.2g) (Macleods)	**16.270 (1.497 for 9.2g)**				
Powder for solution – 5.25g sachet	1.500 (Olainfarm)		**1.550**			
CLOFAZIMINE		**Novartis**				
50mg soft-gel capsule	Not included in the GDF catalogue	**Manufacturer did not agree to publish prices**				
LINEZOLID		**Hetero**	**Pfizer**			
600mg tablet	Not included in the GDF catalogue	2.500	**Manufacturer did not agree to publish prices**			
100mg/ml powder for suspension	Not included in the GDF catalogue		**Manufacturer did not agree to publish prices**			

ANNEX 2: CONDITIONS OF OFFER, AS QUOTED BY COMPANIES

Definitions of eligibility vary from company to company. The conditions detailed in the table below were those quoted by companies.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
AKORN	No restrictions	No restrictions	Akorn is the sole US manufacturer for capreomycin 1g powder for injection and is FDA approved in the United States. Akorn has the capacity to produce 2 million units annually	Ex works
CHAO CENTER (Purdue)	No restrictions	No restrictions		Ex works
CIPLA	No reported restrictions but higher prices have been negotiated separately for ten Latin American countries	No restrictions	Prices for larger quantities are negotiable	FOB (Mumbai, India)
FATOL	No restrictions	No restrictions		Ex works
HETERO				Ex works
JACOBUS	No restrictions unless by US Government	MSF, WHO, GDF	All other organisations will be handled on a case-by-case basis	Ex works
MACLEODS				FCA (Mumbai)
MEDOCHEMIE	No restrictions	No restrictions		Ex works
MICRO LABS	No restrictions except India	No restrictions		Ex works
OLAINFARM	No restrictions	No restrictions		Ex works
PANPHARMA	Cambodia, Latvia, Lithuania	WHO, ICRC, IDA, MSF		Ex works

For more information on incoterms, please refer to the glossary.

ANNEX 3: COMPANY CONTACTS

This section reports the contact details of companies that have been contributing with price information to this publication.

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Chao Center (Purdue)
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FATOL Arzneimittel
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Continued overleaf ⋯

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GLOSSARY AND ABBREVIATIONS

ANDA: 'Abbreviated New Drug Application'. An Abbreviated New Drug Application (ANDA) contains data that, when submitted to the US FDA, provides for the review and ultimate approval of a generic drug product. These applications are 'abbreviated' because they generally are not required to include preclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e. performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low-cost alternative in the US.

API: 'Active pharmaceutical ingredient'. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form.

Clinical trials: Sets of tests in medical research and drug development that generate safety and efficacy data (including information about adverse drug reactions and adverse effects of other treatments) for health interventions (e.g., drugs, diagnostics, devices, therapy protocols).

Compassionate use: The terms 'compassionate use,' 'expanded access' or 'special access' programmes all refer to programmes that are intended to provide potentially lifesaving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists, and/or who cannot enter a clinical trial. The terms refer to programmes that make medicinal products available either on a named patient basis or to cohorts of patients. Compassionate use needs to be framed within a national legislation which establishes the conditions under which the drug is made available. Refer to Annex 5 (Use of experimental drugs outside of clinical trials, "compassionate use") of the WHO Guidelines for the programmatic management of drug-resistant TB, Emergency Update 2008.

Culture: Bacterial culture is a laboratory method used to grow and multiply bacteria in order to determine their presence or otherwise in a sample; it is the gold standard test to diagnose TB.

Drug resistance: Bacteria (in TB, typically M. tuberculosis) which resist a drug's curative or bacteria-killing power.

Drug-susceptible/drug-sensitive TB: Bacteria are said to be sensitive to a drug when the drugs are effective in killing or stopping the multiplication of bacteria in the body and can therefore clear the infections. Strains of TB which are sensitive to all first-line drugs are called drug-susceptible.

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

ERP: 'Expert Review Panel'. An independent technical body composed of external technical experts, hosted by the WHO Department of Essential Medicines and Pharmaceutical Policies. Their purpose is to review the potential quality risk of using antiretroviral, anti-TB and antimalarial products which are not yet WHO prequalified or authorised by a stringent regulatory authority, and to give advice to the Global Fund and the Global Drug Facility whether procurement of such products can be authorised.

Extemporaneous preparation/ formulation: Preparation of a drug product according to a physician's prescription, a drug formula, or a recipe. Extemporaneous preparations are used when the needs of individual patients cannot be met by the use of an approved commerical drug product.

Extensively drug-resistant TB: see XDR-TB

Extra-pulmonary TB: Form of TB where *M. tuberculosis* bacteria infect parts of the body other than the lungs. The most common forms of extra-pulmonary TB affect the lymph nodes, bones, central nervous system, and cardiovascular and gastrointestinal systems.

FCA: 'Free Carrier'. A commerical (Incoterm 2010) term meaning that the seller hands over the goods, cleared for export, into the disposal of the first carrier (named by the buyer) at the named place. The seller pays for carriage to the named point of delivery, and risk passes when the goods are handed over to the first carrier.

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

FOB: 'Free on board'. A commerical (Incoterm 2010) term meaning that the seller delivers when the goods pass the ship's rail at the named port of shipment. This means that the buyer has to bear all costs and risks of loss or damage to the goods from that point. The FOB term requires the seller to clear the goods for export.

GDF: 'Global Drug Facility'. A mechanism hosted by WHO to expand access to, and availability of, quality-assured anti-TB drugs and diagnostics through pooled procurement. Products procured comply with the GDF's Quality Assurance policy. This deems eligible for GDF procurement all products that are included on the WHO List of Prequalified Medicinal Products, that are approved by a stringent regulatory authority, or that are approved by the Expert Review Panel also used by the Global Fund.

Global Fund: The Global Fund to Fight AIDS, Tuberculosis and Malaria is an international financing institution that invests government and private money in HIV, TB and malaria treatment programs. It supports large-scale prevention, treatment and care programs against the three diseases in 150 countries and it channels 82% of the international financing for TB. www.theglobalfund.org

Continued overleaf

GLC: 'Green Light Committee'. The GLC Initiative was created in 2001 to help countries gain access to quality-assured second-line anti-TB drugs so they can provide treatment for people with MDR-TB in line with WHO guidelines, the latest scientific evidence and country experiences. The Initiative consisted of a secretariat, the Green Light Committee (an expert review and WHO advisory body) and the Global Drug Facility (the drug procurement arm of the Initiative). Since 2011, there is no need for GLC approval to procure quality-assured second-line TB drugs through GDF. GLC was restructured in June 2011 into a Global GLC (gGLC) and regional GLC (rGLC) to focus on monitoring and technical assistance to national TB programmes in countries and WHO.

Microscopy: Currently the most commonly used technique to diagnose TB. Two to three sputum samples are taken from the patient, with the sample stained and later read under the microscope. If TB bacilli are present, they will appear highlighted from the rest of the sample.

MDR-TB: 'Multidrug-resistant TB'. Strains of TB that are resistant to (at least) the two most powerful first-line drugs used to treat TB, namely rifampicin and isoniazid, are said to be multidrug-resistant TB, or MDR-TB.

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

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

New Drug Application (NDA): An application to the US FDA to register a new drug for marketing approval; this can only occur once the drug meets requirements on quality, safety, and efficacy. The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed (sold) in the United States.

Pharmacokinetic (PK): Branch of pharmacology, which studies the mechanisms of absorption and distribution of an administered drug; the rate at which a drug action begins and the duration of the effect; the chemical changes of the substance in the body (e.g. by metabolic enzymes); and the effects and routes of excretion of the metabolites of the drug.

Pharmacodynamic (PD): Branch of pharmacology, which studies the biochemical and physiological effects of drugs on the body, or on microorganisms or parasites within or on the body, and the mechanisms of drug action and the relationship between drug concentration and effect.

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

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

QT Interval: In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. This represents the total duration of electrical activity of the ventricles. A prolonged QT interval is a biomarker of life-threatening ventricular tachyarrhythmias – including torsdes de pointes.

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

Stringent regulatory authority (SRA): A regulatory authority which meets criteria principally through membership of, or links to, the International Conference of Harmonization (ICH). Please consult http://www.ich.org

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

Tentative FDA approval: Tentative FDA approval is awarded by the US FDA to a drug product that has met all required quality, safety and efficacy standards, but is not eligible for marketing in the US because of existing patent protection.

Totally drug-resistant (see XDR-TB): The term 'totally drug-resistant TB' was used in 2011 for a group of patients in India who presented with resistance to all known TB drugs they were tested for. It is a term widely by the media, but is not recognised by WHO, after a decision taken during a meeting in 2012 to discuss the term. These cases are defined as extensively drug-resistant tuberculosis (XDR-TB), according to WHO definitions.

US FDA: United States Food and Drug Administration.

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

w/w – Percentage weight/weight: A form of measurement written as x% w/w that indicates the amount of solute (as liquid, granules, powder, etc) that needs to be dissolved – usually in 100mg or mL amounts – to achieve the desired solution strength. For example, a solution written as 20% w/w will mean 20g or 20mL dissolved in 100mL of water.

XDR-TB (Extensively drug-resistant TB): Strain of MDR-TB that also shows resistance to second-line drugs, including at least one fluoroquinolone drug and one injectable drug.

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DR-TB Drugs Under the Microscope – The Sources and Prices of Medicines for Drug-Resistant Tuberculosis is a pricing guide and cannot be regarded as a company price list nor as a clinical guideline. It is crucial that any purchaser verify prices and availability as well as quality status directly with the supplier before procurement. Médecins Sans Frontières or The Union have made every effort to ensure the accuracy of prices and other information presented in this report, but MSF or The Union make no representations or warranties, either expressed or implied, as to their accuracy, completeness or fitness for a particular purpose. Inclusion of a product in this document does not indicate MSF or The Union purchases or uses the product. Information in this guide is indicative only and not exhaustive, and should be verified with relevant offices when used for other than reasons of general information. Clinical decisions should not be made based on this document.

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