DR-TB drugs under the microscope

The sources and prices of medicines for drug-resistant tuberculosis

Tuberculosis (TB) is a curable disease that continues to kill nearly 1.3 million people[1] across the globe each year, and is the main cause of death in people living with HIV/AIDS in Africa[2]. Of the 9.4 million new tuberculosis cases each year, 440,000[3] are forms of the disease that are multidrug-resistant. Over the last decade, roughly five million people developed drug-resistant TB, but less than 1% had access to appropriate treatment[4], and 1.5 million died.

DR, MDR, XDR, PDR: 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 of the common first-line drugs. **Multidrug-resistant tuberculosis** (MDR-TB) is defined by TB that is resistant to isoniazid and rifampicin, the two most powerful anti-TB drugs. Patients who have **extensively drug-resistant tuberculosis** (XDR-TB) are infected with 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 problems that plague DR-TB medicines

This report provides an overview of the available DR-TB medicines, and provides relevant information for each product, including its sources, quality status and price. This information can aid treatment providers, treatment programmes and national procurement centres in making procurement decisions. A number of important problems that hamper access to medicines are brought to light.

The drugs examined in this report are those medicines classed as groups 2-5 of the World Health Organization's 2008 Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Certain problems are more relevant to some drug classes than others.

GROUPING	MEDICINES
Group 1 – First-line oral agents	isoniazid*, rifampicin*, ethambutol*, pyrazinamide*, rifabutin*
Group 2 – Injectable agents	kanamycin, amikacin, capreomycin, streptomycin*
Group 3 – Fluoroquinolones	moxifloxacin, levofloxacin, ofloxacin
Group 4 – Oral bacteriostatic second-line agents	ethionamide, protionamide, cycloserine, terizidone, p-aminosalicylic acid (PAS)
Group 5 – Agents with unclear efficacy	clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid*, b clarithromycin

* this report does not include first-line oral or first-line injectable agents, or high-dose isoniazid

How countries procure DR-TB drugs

In response to a growing need for DR-TB treatment – and to prevent further drug resistance developing through the improper use of DR-TB drugs – the World Health Organization, together with its partners in the Stop TB Partnership, created the 'Green Light Committee' Initiative (GLC) in 2000. The core function of the Green Light Committee has been to provide technical review of proposed DR-TB treatment projects, and 'green-light' them if they meet certain specifications. Approved projects then get access to quality-assured drugs at reduced prices – for a few years now, these have been procured through the WHO-hosted Global Drug Facility.

Today, programmes without GLC approval are not allowed to turn to the Global Drug Facility to access WHO quality-assured drugs. Nearly one decade on, only 13% of the estimated DR-TB drug market is channelled through the Global Drug Facility. In 2010, only 6,000 patients were enrolled in GLC-approved treatment programmes, compared to an estimated 440,000 new cases and 150,000 deaths[5].

1. Limited number of quality sources

Few quality-assured producers exist. For many DR-TB drugs, such as capreomycin, prothionamide, terizidone, PAS and clofazimine, only one quality-assured source[1] exists. For others, including ethionamide, moxifloxacin and PAS-Sodium, there are only two quality-assured sources. Although there has been some recent progress - with a decrease in the number of products that had only one supplier, down from 11 in 2008 to four in 2011[6] - for all of these medicines, supply is extremely vulnerable to disruption.

The example of kanamycin illustrates the risks. In the past, several manufacturers had kanamycin registered for use in the US, although all but one subsequently ceased production because of falling demand in wealthy countries. Today, only three quality-assured sources are identified. Of those, the first was forced to suspend production because of the relocation of its supplier of active pharmaceutical ingredient in 2009. The second also experienced a supply problem in 2010 and ceased production, leaving programmes dependent on a third manufacturer with limited capacity, so much so that its production is solely dedicated to GDF procurement, leaving other DR-TB treatment programmes with no quality-assured source.

For a number of DR-TB medicines, multiple producers in Russia, India, China and other countries are known to manufacture DR-TB drugs, but whether they could comply with WHO or stringent regulatory authority standards is unknown. Part of the problem of too few quality-assured sources could be resolved if manufacturers improved their compliance with internationally recognised quality standards and submitted product dossiers for quality evaluation.

Sources of active pharmaceutical ingredients are limited. Increasing the number of quality-assured sources for some DR-TB drugs is to a large extent due to the difficulties associated with the production of the active pharmaceutical ingredient (API). For several drugs, such as capreomycin and kanamycin, only one quality-assured API source has been identified. In the case of capreomycin, all quality-assured finished products identified in this document are reliant on a single source of API, again making the entire supply of capreomycin extremely vulnerable to disruption. A recent study for the GDF noted that the supply of API was vulnerable for amakycin, kanamycin, prothionamide and clofazimine[7].

2. Limited affordability

The price of DR-TB treatment varies considerably, as treatment must be individualised according to a patient's drug resistance profile. Drugs procured through the GLC/GDF cost between US$ 4,400 and $9,000 per patient for a standard 18-24 month treatment course. For drugs purchased outside of the GLC/GDF, prices may be even higher. In comparison, first-line TB treatment costs $19 per patient for a six-month treatment course[8]. For drug-sensitive and even more so for drug-resistant TB, to the price of the medicines must be added significant costs in terms of human resources for medical and psychosocial care, and treatment to counter side effects. As the cost of DR-TB treatment is considerably more expensive, this acts as a barrier to treatment scale up.

[1] For the purpose of this report, quality-assured medicines are those included on the WHO List of Prequalified Medicinal Products or approved by what is known as a stringent drug regulatory authority such as the US Food and Drugs Administration. Such quality approval is a requirement by donors financing MDR-TB programmes such as UNITAID or the Global Fund to Fight AIDS, TB and Malaria.

These prices are a reflection of insufficient market competition among multiple producers, both at the level of API production, as well as at finished product level. They are also a consequence of limited demand for DR-TB drugs, as with low volumes, manufacturers cannot hope to achieve economies of scale necessary to bring prices down. This is one area where a new diagnostic test, by diagnosing more effectively and more quickly patients with DR-TB, will increase demand for more second-line anti-tuberculosis medicines.

The price of four medicines in particular weigh heavily in the overall cost of a DR-TB regimen. Overall costs of the DR-TB regimen are particularly driven by capreomycin, moxifloxacin, PAS and cycloserine.

For most DR-TB drugs, patents are not typically a factor in causing high prices, because the medicines were developed so long ago that patents on most have long run out. However, moxifloxacin is a notable exception – until now, Bayer's monopoly has kept prices high.

Some DR-TB drug prices have increased considerably between 2001 and 2011, including for the medicines procured through the GDF for GLC-approved treatment programmes. This is true of the prices of amikacin (the most affordable source in 2011 costs eight times more the most affordable source in 2001), kanamycin (six times more), cycloserine and capreomycin (both three times more).

For kanamycin, the hike in price is due to GDF turning to Meiji after supply problems affected the production of more affordable versions. For capreomycin and cycloserine, this rise in price is explained by the fact that Eli Lilly has ceased production, and put an end to the subsidised prices it was offering the GLC. Since 2003, the US company has been actively engaged in technology transfer to generic manufacturers, and those who now produce charge substantially higher prices.

3. The neglect of children and people living with HIV

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[9]. Yet only two medicines featured in this report (amakycin and levofloxacin) have been developed as paediatric formulations, and these are not widely available. This means that treatment providers who attempt to treat children must do so by manipulating adult formulations, such as breaking or crushing tablets to approximate the required dose for a child. This carries a major risk or over- or under-dosing a child. In addition, safety and efficacy data in children have not been established for all but three of the medicines used in DR-TB treatment.

The interactions of DR-TB drugs with AIDS medicines are also largely unknown. There is precious little information on how DR-TB drugs interact with antiretroviral medicines used to treat HIV/AIDS[10] – this has not been a priority for developers of HIV drugs as co-infection with TB is today uncommon in wealthy countries. This is particularly problematic given that TB is the biggest killer of people living with HIV today[11].

R&D for TB: A long story of neglect

The medicines used in DR-TB treatment cause often intolerable side effects, which can include severe vomiting, depression, hallucinations, and hearing loss. Until today, there has been very little research to even determine the best use of existing drugs. In fact, today's treatment for DR-TB is largely based on experience and expert opinion, not studies or clinical trials, with a large number of 'grey areas' where expert opinions may be conflicting[12].

With so many complaints associated with drug-resistant tuberculosis treatment, many look to the research and development (R&D) pipelines for a new regimen to answer these problems. Yet TB

R&D was neglected for decades because the disease primarily affects developing countries and therefore did not represent a lucrative market for the pharmaceutical industry.

After having been at a virtual standstill for about 40 years, the TB drug pipeline has seen encouraging progress in recent years[13]. However, no new drug has yet reached the market. Tibotec's TMC 207 is expected to get accelerated approval for use in DR-TB treatment as early as 2012.[14] But further studies will be needed to determine whether adding the new drug will allow some of the older drugs to be removed from the regimen and how much the treatment can be shortened.

The current objective of the TB Alliance, the leading product development partnership in TB drug R&D, is to deliver a new short regimen able to treat both drug-sensitive and drug-resistant TB, and also compatible with HIV treatment[15]. While there is wide agreement on this mid- to long-term objective, it is questionable whether this objective can be achieved within reasonable timelines. The most urgent priority has to be to improve treatment of MDR-TB, given length, toxicity and limited effectiveness of current treatment.

It is also crucial to make today's DR-TB treatment as tolerable as possible for patients. This entails conducting studies on how to alleviate the worst side effects caused by existing drugs by, for example, looking at ways to space the intake of drugs, optimise doses, develop alternative, more user-friendly formulations and study their use in children and people living with HIV.

Conclusions: breaking the vicious circle

With insufficient numbers of patients on treatment, demand for DR-TB drugs is low, and the market for the development and production of DR-TB drugs remains unattractive. This creates a vicious circle because limited drug supplies in turn contribute to hindering the scale up DR-TB treatment. As demand stays low, not least for WHO quality-assured drugs, there is little incentive either for new producers to enter the market or for existing producers to invest in meeting WHO quality standards or increasing production capacity. Supply insecurity due to delivery delay or interruption - as for kanamycin in 2010 – 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. Untreated DR-TB further encourages the disease's spread.

Low demand for DR-TB drugs is also caused by the difficulties surrounding diagnosis – only 7% of 440,000 new MDR-TB cases were detected in 2008. Until now, it has taken up to three months to determine a patient's precise drug-resistance profile, and diagnosis of TB is especially complicated in both people living with HIV/AIDS and children.

However, a new diagnostic tool based on molecular technology, Xpert MTB/RIF, could help break open the vicious circle by dramatically shortening the time it takes to determine whether someone has TB to 90 minutes. It can also determine whether a patient is resistant to one of the main first-line drugs to treat TB. Endorsed in December 2010 by the World Health Organization, the test is being rolled out in MSF programmes in 15 countries this year. If Xpert MTB/RIF is implemented more widely, improved diagnosis could contribute to the level of increased demand needed to make the DR-TB drug market more attractive to drug developers and manufacturers. This, in turn, could lead to additional suppliers entering the market and seeking WHO quality assurance, and prices decreasing.

Targeted interventions are also needed to stimulate the MDR-TB drug market:

- **The Global Drug Facility** should no longer restrict sale of quality-assured medicines to GLC-approved programmes. All treatment programmes should be able to buy quality-assured medicines;
- The GDF should further develop and pursue the activities outlined as a part of its 'Roadmap for MDR-TB Scale Up',[16] which lists a number of market interventions to attract new suppliers. This includes an advance purchase commitment to give manufacturers binding

long-term orders that would act as financial incentives for greater production, and the expansion of the existing rotating stockpile to decrease the time it takes for countries to receive medicines;

- **Manufacturers and drug developers** should invest in production and WHO prequalification of existing DR-TB drugs, including paediatric formulations, anticipating an international treatment scale up;
- Drug developers currently investing in the development of new TB drugs should trial their compounds in DR-TB patient populations. Efforts should be undertaken to make new drugs available as quickly as possible via compassionate use and expanded access programmes;
- **Countries affected by TB** should make scale up of DR-TB treatment a priority with investment in increased diagnostic capacity and dramatically increased and more rapid enrolment of patients on treatment. Innovative models for community based treatment that allow to reach more patients and better are showing good results and should be supported[17];
- Countries affected by TB should make a commitment to purchase only quality-assured medicines. This will benefit patients and act against further resistance development but will also help to create increased economies of scale for quality-assured products;
- High-level support is needed in many high-burden countries to ensure fast track registration of DR-TB drugs or fast-track mechanisms for importation;
- **Donors** have an important role to play to guide and support financially the market interventions needed to improve international DR-TB drug supply and reduce prices;
- Donors' support will be critical to ensure the international treatment scale-up, although many DR-TB high-burden countries have contributed and need to continue contributing significant resources to MDR-TB programmes. It has been estimated that $16.2 billion are needed between 2010-2015 to support treatment in the 27 high-burden countries[18]; and
- Donors should support research to define a better and shorter DR TB treatment regimen with the inclusion of newer drugs.

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