UNITAID

2014

Tuberculosis Medicines Technology and Market Landscape

CONTENTS

Figures

Abbreviations

ACTG	AIDS Clinical Trials Group
AIDS	acquired immunodeficiency syndrome
API	active pharmaceutical ingredient
ARV	antiretroviral
BRICS	Brazil, Russian Federation, India, China and South Africa
CDC	Centers for Disease Control and Prevention (United States)
CIHR	Canadian Institutes of Health Research
DDI	drug–drug interaction
DR TB	drug-resistant tuberculosis
DS TB	drug-susceptible tuberculosis
DST	drug susceptibility testing
EDCTP	European & Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
ERP	Expert Review Panel
FDC	fixed-dose combination
g	gram
GDF	Global Drug Facility
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HIV	human immunodeficiency virus
INR	Indian rupee
IPT	isoniazid preventive therapy
kg	kg
LTBI	latent TB infection
MDR TB	multidrug-resistant tuberculosis
mg	milligram
ml	millilitre
MTB	*Mycobacterium tuberculosis*
NIH	National Institutes of Health (United States)
NTP	national tuberculosis programme
OFLOTUB	Gatifloxacin for TB (formerly OFLOxacin-containing TUBerculosis regimen)
OST	opioid substitution therapy
PanACEA	Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics
PAS	para-aminosalicylic acid
PPM	public–private mix
PQ	Prequalification of Medicines Programme (WHO)
PQR	Global Fund to Fight AIDS, Tuberculosis and Malaria's Price & Quality Reporting Tool
QA	quality-assured
STREAM	Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multi-drug Resistant Tuberculosis
TB	tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TBTC	Tuberculosis Trials Consortium
UK MRC	United Kingdom Medical Research Council
US FDA	United States Food and Drug Administration
USAID	United States Agency for International Development
US$	United States dollar
VAT	value-added tax
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis
ZAR	South African rand
°C	degrees Celsius

FOREWORD

Tuberculosis (TB) is a curable disease, but among the 8.6 million new cases in 2012, there were 1.3 million deaths. Currently available medicines can cure most cases of TB in six months, and advances in technology—including novel and repurposed medicines and regimens—hold promise as new or improved tools to treat drug-resistant forms of the disease. However, many patients do not have access to appropriate TB medicines. Lack of access can be traced, in large part, to markets that do not function well. For example, problems such as high prices and supply vulnerability can be caused by fragmented, low and variable demand, a limited number of suppliers, and other factors. TB medicines are procured through many channels, with significant procurement by national governments and in the private sector—that is, outside of the donor-funded market. As a result, unconventional approaches may be required to improve access to TB commodities, particularly at the point where patients seek care. Despite existing medicines and expected future innovations, there is a persisting need to improve market function to increase patients' access to appropriate TB medicines—particularly in the areas of multidrug-resistant TB (MDR TB) and paediatric TB. Market-based approaches will be pivotal in addressing this need.

To inform potential opportunities for market intervention, this report reviews the following: the public health problem of TB; access issues related to TB medicines; TB technology and market landscapes; and market shortcomings. Potential opportunities for TB medicines market interventions may include: evidence-generation required to improve access and consolidate demand; support for forecasting and procurement; product-specific work on active pharmaceutical ingredients (APIs) and finished pharmaceutical product markets; and stakeholder coordination to optimize access to appropriate tools. Key highlights of this edition of the landscape, informed by analysis of recent market trends and close collaboration with partners, include challenges and opportunities related to: new drugs and regimens in development; market fragmentation; and manufacture of specific products.

This report is just one part of a broad and ongoing effort by UNITAID to understand the landscape for TB medicines, and should be considered alongside other tools and initiatives. As data on TB medicines markets are incomplete, UNITAID intends this report to serve primarily to stimulate discussion—at the UNITAID 2013 Tuberculosis Market Forum (see Box 3) and other interactions with partners. That is, this report should be considered a *preliminary* analysis to: (i) engage key stakeholders in discussion of critical market shortcomings related to TB medicines; and (ii) identify potential market-based approaches to remedy these and establish or restore functional market dynamics.

EXECUTIVE SUMMARY[1]

The public health problem of tuberculosis (TB) and access issues related to TB medicines
A serious threat to public health worldwide, TB caused 1.3 million deaths in 2012 alone. Although largely curable, TB remains a leading cause of death in people co-infected with HIV and among women of reproductive age. The burden of TB is also borne disproportionately by the most vulnerable populations: the highest TB death rates are in low-income countries, and TB is one of the top 10 causes of death in children. Access to appropriate, quality-assured (QA) medicines—critically lacking in so many resource-limited settings—is vital for the control of TB.

In 2012, about 3 million people with active TB—one third of all new cases—were not reported and likely not treated according to World Health Organization (WHO) recommendations. Access for TB patients infected with drug-resistant strains is even lower: in 2012, about 77 300 patients (of an estimated 450 000 total) were enrolled on second-line treatment. Access to TB care for children is poor: recent studies have reiterated assumptions that approximately 1 million children may need TB treatment each year, yet only 349 000 paediatric TB cases were reported to national programmes in 2012. And even when paediatric TB is detected and treated, available formulations of TB medicines are inappropriate for children and not aligned with WHO recommendations.

TB medicines technology landscape
Review of the technology landscape highlights the developments and gaps in the TB medicines pipeline towards addressing challenges to current TB treatment. These challenges include: long duration of treatment for latent, drug-susceptible TB (DS TB) and drug-resistant TB (DR TB); low cure rates and poor tolerability for DR-TB treatment; drug–drug interactions; and a lack of proven preventive options for contacts of people with DR TB.

This section places an emphasis on recent developments in TB medicines, including the marketing authorization of delamanid in Europe, and further regulatory approvals of bedaquiline, after 40 years without approval of a new drug class in TB. The technology overview analyses the potential role of these two new medicines, as well as other candidates in the pipeline such as PA-824, sutezolid and AZD5847, in improving TB treatment as novel agents added to existing therapy, or as part of new regimens.

Emphasis is also placed on examining efforts to optimize the use of existing medicines to improve TB therapy. New data on fluoroquinolones' role in treatment-shortening indicate that other strategies are likely necessary to bring treatment for DS TB to four months or less; these may include higher doses of rifamycins, which appear promisingly safe and potent. The STREAM study is examining whether seven widely available medicines can be combined to shorten treatment for multidrug-resistant TB (MDR TB) to nine months. Existing medicines such as rifampicin and rifapentine offer promise to shorten treatment for

---

latent TB infection (LTBI), and levofloxacin will be examined for treating LTBI in contacts of people with DR TB, who currently have no validated options to prevent the development of active disease.

TB medicines market landscape
The total value of the TB medicines market in 2012 (public and private sectors) is estimated to be approximately US$ 700 million, including up to US$ 425 million for first-line treatment of TB in adults and US$ 300 million for treatment of MDR TB in adults. Estimates are uncertain, particularly for children—a segment probably worth less than US$ 10 million globally in 2012.

There is no single dominant purchaser of TB medicines overall.[2] Instead, the market is fragmented across donors, government purchasers and the private sector. National governments are significant purchasers of first-line drugs and, increasingly, of MDR-TB drugs. The private sector, too, plays an important role, but visibility on this market segment is poor: market size, treatment patterns and other dynamics have been characterized to some extent in middle-income countries, but are very poorly understood in low-income countries.

Market fragmentation is a continuing challenge in complex TB medicines markets—driven by: multiple purchasers, each with procurement requirements and tender processes that can be unique to each purchaser; and market complexity (i.e. too many regimens used and/or excessive variation in medicines formulations). While there may be scope for simplifying treatment, some of the variation in TB medicines is clinically necessary. Further evidence is needed to understand where streamlining may be possible, thus helping to stabilize TB medicines markets.

First-line medicines to treat DS TB in adults constitute the largest market segment by volume and value—a segment that is relatively stable and characterized by mostly generic, low-cost products. Treatment of MDR TB in adults and treatment of TB in children represent much smaller segments of the TB medicines market by volume, relative to first-line treatment in adults. Although MDR-TB medicines are much more expensive than those used for first-line treatment (US$ 1800–6000 + versus US$ 22 per regimen), and treatment duration is longer (20–24 versus 6 months), volumes are extremely low (though growing). The market for paediatric TB medicines is similarly small, fragmented and fragile. These market segments are complex and fragile, with numerous and severe market shortcomings.

Market shortcomings related to TB medicines
Market shortcomings related to TB medicines include issues of availability, affordability, quality, acceptability/adaptability, and delivery. Market shortcomings related to TB medicines are especially pronounced for MDR TB (Table 1) and paediatric medicines (Table 2). For example, MDR-TB regimens are complex, expensive, long term (20–24 months, including 8 months of injections), and can have severe side-effects. QA MDR-TB drugs are expensive, and make up only a fraction of the global market for these drugs. TB medicines are especially prone to supply shortages and stock-outs—in part due to unstable supply of raw input materials and unpredictable demand—and inappropriate medicine selection and use can occur, particularly in the private sector. The lack of appropriately dosed, QA, paediatric TB fixed-dose combinations (FDCs) makes it harder for health-care workers to provide the correct dosages and likely means that many children receive treatment inconsistent with WHO guidelines.

---

2 For certain market segments, there are dominant, key players (i.e. in the public sector, GDF accounts for 29% of the first-line market and 39% of the second-line market).

Table 1. Market shortcomings related to MDR-TB medicines

Market shortcoming and description	Reason
Availability: Lack of short, effective, streamlined MDR-TB regimens (current regimens are complex and expensive; last 20–24 months, including 8 months of injections, and have severe side-effects)	■ Limited market incentives: small target population, diminished further by underdiagnosis and low enrolment ■ Inherent high risk in new drug development as resistance evolves; one-at-a-time approach to drug development employed by most manufacturers means development of novel regimens is challenging; long, complex studies required due to lack of an accurate surrogate marker for treatment success
Affordability: QA MDR-TB drugs are expensive (e.g. US$ 1800–6000+ per treatment course for a standard 24-month regimen)	■ Manufacturing costs driven by complex production (injectables), quality assurance requirements, low total volumes and unpredictable demand, lengthy procurement processes and market fragmentation ■ Increased (since 2012) but still limited competition: few suppliers exist for finished products and active ingredients ■ Price increases due to manufacturer exit and product shortages
Quality: QA medicines account for only a fraction of the total market	■ Limited market incentives for producers to invest in stringent regulatory approval ■ TB medicines purchased in the private sector or through NTPs can be of variable or unknown quality as some domestic procurers may prioritize price or other factors over quality assurance
Acceptability/adaptability: Long-term regimens (especially for MDR TB) increase costs and decrease adherence	■ Limited market incentives for developers to invest in clinical trials for new TB medicines (existing first-line regimen is high volume but cheap; MDR-TB treatment is expensive but low volume)
Delivery: Low uptake of MDR-TB drugs, with fewer than one in five patients receiving appropriate treatment	■ Low availability of DST (~5% of patients in 2012)[1] limits number of MDR-TB cases detected and treated appropriately ■ MDR-TB treatment is long, burdensome, expensive, and prone to supply interruptions—reducing adherence and contributing to low uptake ■ Some NTPs have historically focused more on first-line than MDR-TB
Delivery: Supply shortages, stock-outs, and long and variable lead times	■ Limited number of suppliers, especially of APIs ■ Lack of reliable forecasting of MDR-TB treatment numbers—in part due to difficulty in planning and predicting speed of scale-up of DST, which leads to low and variable demand, and in turn drives "made-to-order" production
Delivery: Inappropriate medicine selection and use in the private sector	■ Inappropriate prescribing by private-sector physicians, in part due to the lack of access to a full range of MDR-TB medicines in the private sector and lack of enforced quality standards

Sources and notes: Refer to section 6.5.1 for details.

---

1 Driven in turn by insufficient history-taking to identify clients who are at high risk of MDR TB and, therefore, a high priority for drug-susceptibility testing.

Table 2. Market shortcomings related to paediatric TB medicines

Market shortcoming and description	Reason
Affordability: Paediatric TB medicines are more expensive than those for adults, despite containing less active ingredient	■ Few suppliers for QA formulations ■ Increased risk for manufacturers: small market; fragmented demand; and higher development costs
Quality: Many children receive unknown-quality drugs in non-standard doses (e.g. split adult FDCs)	■ No QA, appropriately dosed FDCs (i.e. FDCs that correspond to the dosing recommended in the 2014 WHO revised guidelines) exist ■ Private-sector and non-donor public-sector procurement can have varying quality standards
Acceptability/adaptability: No appropriately dosed, QA, paediatric FDC on the market consistent with 2014 WHO treatment guideline revision Delays in needed paediatric trials for novel medicines Of MDR-TB drugs, only amikacin, levofloxacin and linezolid have been developed for children, but even these are often not widely available or are for non-TB indications	■ Small, fragmented QA paediatric market is less attractive to developers (i.e. low return on investment due to very limited demand) ■ Additional costs of product development ■ Uncertain regulatory and quality requirements
Delivery: Supply shortages, stock-outs and long lead times	■ Limited number of suppliers of QA appropriate formulations ■ Lack of reliable forecasting and low and variable demand
Delivery: TB diagnostics are not appropriate for children; 90% of children with TB is smear negative, and specimen collection in children is challenging	■ Smear microscopy is not suited for children because: it requires sputum, which is difficult to collect in children; children have low levels of bacteria in sputum; and children are prone to extrapulmonary TB

Sources and notes: Refer to section 6.5.2 for details.

Potential opportunities for TB medicines market interventions

TB medicines markets are complex, fragmented and subject to a wide range of market shortcomings—making design of market-based interventions challenging. Multiple or stepwise approaches may be required. Given close links between market segments and the importance of a diverse range of stakeholders procuring TB medicines, complementary approaches and careful coordination between partners are key to success.

Potential opportunities for market-based intervention in TB medicines markets may include work to:

■ Generate evidence to improve and simplify MDR-TB treatment and consolidate demand—e.g. inform choices within drug classes or regimen composition; identify and reduce non-essential variation; support early determination of target product profiles; model costs and impacts of new regimens and related diagnostic tools to better define potential future markets.

■ Support effective forecasting, procurement and supply management—e.g. improve order planning and quantification; increase demand for QA products with demand incentives, technical support or innovative business models; support mechanisms to ensure timely payment.

■ Facilitate healthy markets for TB API and finished pharmaceutical products—e.g. support technical assistance or incentives such as advanced purchase commitments and/or stockpiles to increase volume, enable manufacturing optimization and smooth demand fluctuations.

■ Support coordination of donor and non-donor actors, including the private sector and government—e.g. engage non-donor stakeholders in innovative, sustainable and scaleable ways with social business models, financial and other incentives; support coordinated procurement activities for better market transparency and purchasing power.

■ Support better diagnosis and treatment for children with TB—e.g. consolidate demand, negotiate prices and scale up appropriately dosed, QA paediatric TB medicines, when available; and facilitate development and uptake of TB diagnostics appropriate for children.

1. Introduction

UNITAID works through market interventions to improve access to medicines, diagnostics and preventive items used in HIV/AIDS, tuberculosis (TB) and malaria. UNITAID develops market landscapes as part of a broad effort to characterize the landscape for TB medicines, highlighting critical market shortcomings and potential market-based approaches related to TB medicines.

This document is a landscape analysis of medicines to treat TB, including both existing products and regimens currently in use, as well as emerging technologies with the potential to improve treatment. The purpose of this report is to stimulate discussion and inform potential opportunities for market intervention that could improve access to TB medicines and, ultimately, public health outcomes related to TB. To serve this purpose, this report:

- first, reviews the public health problem of TB, and critical access issues related to TB medicines (sections 3 and 4);
- second, assesses the technology landscape, including TB medicines currently recommended or otherwise commonly used, and recent developments in expected new TB drugs and regimens (section 5);
- third, analyses the market landscape, providing a high-level market overview, with estimates of procurement by type of buyer, and trends in price, competition, supply, etc., for critical TB medicines (sections 6.1 through 6.4);
- fourth, summarizes market shortcomings related to TB medicines, providing the context for next steps and areas of potential intervention (sections 6.5 and 6.6).

By providing a basic characterization of TB medicines markets and preliminary analyses of available data, this report is intended as a starting point for discussion of shortcomings and potential market-based approaches. UNITAID expects that the contents of this report, and the discussion it stimulates, may have utility and relevance beyond UNITAID—particularly for others interested in developing and applying market-based approaches to improve access to TB medicines.

2. Methodology

This landscape was developed from primary sources (e.g. interviews with technology developers; targeted analyses where needed) and extensive review of secondary sources (e.g. published literature and unpublished reports; World Health Organization [WHO] policies and systematic reviews; corporate prospectuses; developer websites; analysis of publicly available procurement data). Further detail on development of specific sections follows.

2.1. Methods to develop public health problem

Section 3, Public health problem, was adapted from material prepared by Kelly Roney, Doris Rouse, Anita Woodring, and Diana SeverynseStevens (RTI International, Research Triangle Park, NC, United States) for the UNITAID 2013 Tuberculosis Medicines Technology and Market Landscape, 1st edition, updated in 2014 by Megan Paterson for UNITAID.

2.2. Methods to develop commodity access issues

Section 4, Commodity access issues, was developed in-house at UNITAID, based on analysis of available literature and reports to quantify the gap between need, diagnosis and enrolment on treatment, and updated in 2014 by Megan Paterson for UNITAID.

2.3. Methods to develop technology landscape

The Treatment Action Group developed the technology Landscape material in section 5.2 to review products and strategies currently in development, with a particular focus on recent changes (from late 2013 to June 2014) to the TB medicines pipeline; regulatory, normative guidance and access plans; and other developments that may influence the TB medicines market. The Treatment Action Group's Erica Lessem and Colleen Daniels developed the technology landscape material, with assistance from Lindsay McKenna and Lauren Volpert. Authors compiled this material describing current and future products using information in the public domain—including published and unpublished reports and articles, peer-reviewed publications, country and global normative guidance, regulatory and developer websites, mainstream media articles, and clinicaltrials.gov and United States Food and Drug Administration (US FDA) databases. Information not in the public domain was gathered from correspondence with TB drug developers and researchers and was confirmed via draft review with sources. Emphasis was placed on new material from late 2013 to June 2014, and is current to June 2014 unless otherwise specified. This work was completed with support from UNITAID.

Section 5.1, Technology overview: current available medicines and treatment guidelines, was compiled from existing global recommendations on TB care and control and authored by Brian Kaiser and Megan Paterson for UNITAID.

Figure 4 was provided courtesy of Partners In Health.

Figure 5 was adapted by Mengyan Li for UNITAID, using data from the Global TB Drug Pipeline, Working Group on New TB Drugs, and section 5 content; with input from Erica Lessem, Treatment Action Group, and Megan Paterson.

2.4. Methods to develop market landscape

The market assessment for this report (section 6) was compiled in-house at UNITAID by Janet Ginnard, with exceptions described in Boxes 1–6. Contextual material in this report was gathered from publicly available information and published and unpublished reports and articles. Market overview analytics were informed by multiple sources. Global volume estimates were derived from analysis of WHO publications. Value estimates by procurement channel (as shown in Figure 1 and described below) were derived from analysis of various sources by Janet Ginnard with support from Philippa Crompton, Mengyan Li and Megan Paterson for UNITAID (refer to Appendix 1, Additional detail on methods for select figures and tables, for further detail).

Figure 1. TB medicines procurement channels cited in this report
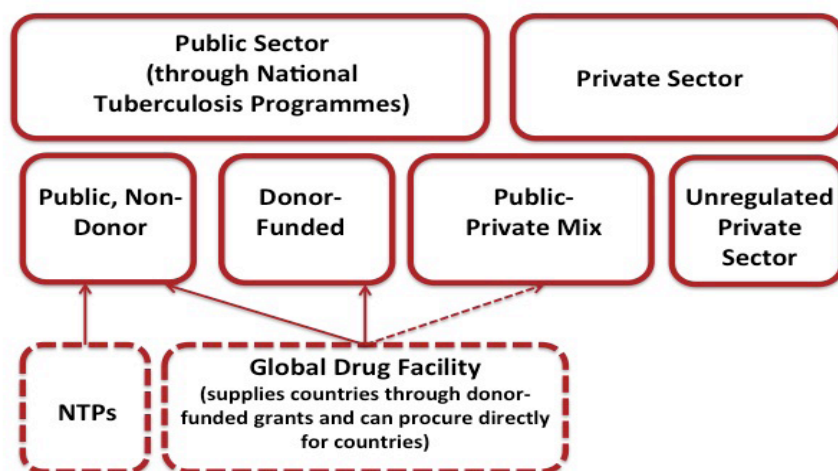
Note: Illustrative, for the purpose of defining segments in this report only. Not indicative of relative market share. For a more detailed illustration of the procurement channels, please refer to Appendix 3, provided courtesy of GDF.

Global Drug Facility (GDF): GDF supports both donor-funded and public non-donor segments shown in Figure 1. That is, GDF supplies quality-assured (QA) TB medicines for the donor-funded segment (i.e. for countries included in donor grants), and also provides direct procurement for countries (i.e. for countries buying TB medicines with their own or other funds). Significant excerpts of transaction-level data were provided by Thierry Cordier-Lassalle (GDF) during development of the previous edition of this report. Given GDF's extensive analysis of its own data, and to avoid duplication of transactions reported elsewhere (see Public sector, donor-funded, below), GDF procurement figures included in this report primarily reflect GDF annual reports, GDF online resources (e.g. product catalogue) or literature.

Public sector, donor-funded: Data were obtained from the Global Fund to Fight AIDS, Tuberculosis and Malaria's Price & Quality Reporting (PQR) Tool, downloaded on 23 May 2014. Records for 152 transactions flagged in the PQR as "pending verification" and listed with a null quantity were excluded from the analytic dataset. The final dataset included 5361 procurements of TB medicines costing over US$ 350 million with purchase order dates from 2007 to 2013.

Public sector, non-donor: This analysis extrapolated data reported to WHO from 99 countries, accounting for 85% of global drug-susceptible TB (DS-TB) cases and 29% of multidrug-resistant TB (MDR-TB) cases receiving treatment. (1) For South Africa only, the analysis used actual tender data. Figures related to South Africa reflect analysis of bids HP01-2013TB and HP01-2013TB/01, supply and delivery of anti-tuberculosis medicines to the Department of Health for the period from 1 August 2013 to 31 July 2015. (2, 3) Historical exchange rates were used, from the date the first contract was signed: 9.9141 ZAR = US$ 1 on 8 June 2013. (4) Where relevant, it was assumed that the 2012 value of TB medicines procured equaled 50% of the total value of the tender over two years. The top-line figure for Indian government MDR-TB medicines procurement (Figure 7) was derived from analysis of public data on Indian government pur-

chases of TB medicines in fiscal year 2011–2012. Data were obtained through requests for information filed by Access Health International for UNITAID. In addition to raw data, support for interpretation and contextualization of these data was provided by Prabal Singh, Anand Tatambhotla and Rohini Rao (Access Health International). (5) Data reflect procurement through RITES with Indian government funds, including World Bank loans, but excluding GDF procurement with donor funds. The exchange rate used was 0.02161 INR = US$ 1 (x-rates.com).

Transactional data on donor-funded purchases and tender data on non-donor public procurement were used to analyse product-specific issues. PQR data (as described above) were analysed to determine directional trends in volume, value, price, supplier concentration, etc. in the donor-funded market for critical MDR-TB medicines. In 2011, the Global Fund provided almost 90% of international donor funding for TB and funded approximately three quarters of the total value of GDF purchases of MDR-TB medicines (US$ 63 million of US$ 85 million). (6) Data from South Africa's recent TB medicines tenders (as described above) were analysed for trends, including supplier concentration, prices, etc., and notable differences from the donor-funded market. Analysis of non-donor-funded Indian government purchases of TB medicines was performed using data obtained as described above. (5)

For analysis of transactional data, purchases in a given year were considered to reflect treatments in that same year—i.e. value estimates for 2012 reflect medicines purchased in 2012, even though an individual patient's treatment would be expected to extend beyond 2012. For analysis of tender data, purchases in a given year were standardized based on the length of the tender period—e.g. it was assumed that 50% of the value of a two-year tender reflected the value of one year of medicines procurement.

Private sector: For first-line TB medicines, country patterns were interpreted from literature (e.g. percentage of patients accessing care through public–private mix [PPM] programmes or in the unregulated private sector; number of treatment regimens procured through PPM programmes or obtained in the unregulated private sector). For MDR-TB medicines, an estimate was derived by deducting the value of donor and public segments (calculated from data analysis, as described above) from 2011 WHO global market estimates. (1)

Content in Box 3 was developed by Janet Ginnard, adapted from the UNITAID 2013 Tuberculosis Market Forum discussion paper, prepared by Jennifer Cohn and Maarten van Cleeff with support from UNITAID and the United States Agency for International Development (USAID).

Content in Box 4 was developed by Janet Ginnard, adapted from content provided by Partners In Health.

Box 5 is an excerpt of a summary authored by Prashant Yadav of the William Davidson Institute. Initial findings were derived from work including quasi-structured interviews with current or potential active pharmaceutical ingredient (API) manufacturers for MDR-TB medicines, empirical models to understand drivers of competition in markets for APIs and process modelling for key MDR-TB medicines.

Box 6 is an excerpt of a report authored by Carole Jefferson, acting as a consultant for UNITAID. Findings reflect literature and website review plus input from TB diagnostic experts.

Section 6.6.1, Potential opportunities for market intervention: DS- and MDR-TB medicines, was adapted from the UNITAID 2013 Tuberculosis Market Forum discussion paper, prepared by Jennifer Cohn and Maarten van Cleeff with support from UNITAID and USAID, updated and adapted based on contents of this landscape document.

Details of analyses for specific charts and tables can be found in Appendix 1, Additional detail on methods for select figures and tables.

3. Public health problem

TB is a communicable airborne disease caused by *Mycobacterium tuberculosis* (MTB), which typically affects the lungs (pulmonary TB), but also can affect other parts of the body (extrapulmonary TB). Transmission occurs by the inhalation of MTB from a person with an active TB infection via microscopic droplets (exhaled into the atmosphere) expelled by coughing, speaking or sneezing. (7) Transmission of MTB most often leads to a latent TB infection (LTBI) that is non-infectious and asymptomatic; an estimated one third of the population has LTBI. (8) However, approximately 5–20% of all latently infected individuals will develop active TB during their lifetime. (9) People living with HIV are considerably more susceptible to TB, being 20–37 times more likely than those who are HIV-negative to develop active TB in any given year. (10, 11)

TB is a serious threat to public health worldwide, declared a global emergency by WHO in 1993. (12) The fight against TB remains a global priority today; most recently with the formal endorsement of the Post-2015 Global TB Strategy and Targets on 19 May 2014 at the 67th World Health Assembly (refer to Box 1). (13) In 2012, 8.6 million incident cases of active TB occurred globally, and 1.3 million TB-related deaths occurred. (7) Prevalence, incidence and mortality rates have remained stable over time, with a slight but steady decrease in prevalence since 2000. TB is the most common cause of death among people co-infected with HIV (14, 15), and the burden of TB has been profoundly affected by the spread of HIV/AIDS (12): approximately 13% of all TB cases and 25% of all TB deaths occurred in people co-infected with HIV, and TB accounts for one quarter of all HIV-related deaths. (7) In addition, TB is the second leading cause of death among women of reproductive age, killing more women than all other causes of maternal mortality combined. (12, 16)

If active TB is left untreated, or if a person has a drug-resistant strain, mortality is high and the infection can remain transmissible. (17) Treatment of DS TB typically takes six months with first-line antibiotic TB medicines (ethambutol, isoniazid, pyrazinamide and rifampicin). MDR TB, on the other hand, is resistant to isoniazid and rifampicin and requires treatment with second-line medicines for at least 20 months. (7) MDR TB continues to be a growing concern, with about 450 000 new cases and 170 000 deaths estimated in 2012. (7) Nearly 10% of the MDR-TB cases also has resistance to two other classes of drugs, resulting in extensively drug-resistant TB (XDR TB). XDR TB is resistant to isoniazid, rifampicin and fluoroquinolone, and at least one injectable second-line drug, leaving limited treatment options. The success rate in treating MDR TB was 50% in 2012, and far lower for XDR TB. (7)

The burden of TB is concentrated in 22 high-burden countries, which account for over 80% of notified cases worldwide. Most TB cases occur in middle-income countries, which accounted for almost three in four incident cases in 2012. (7) In addition, over half of all TB deaths in 2012 occurred in lower-middle-income countries. (7) However, TB mortality rates are highest in low-income countries. Access to TB commodities is unequal—within and between countries—with especially pronounced commodity access issues related to medicines for MDR TB and paediatric TB (refer to sections 4.1 and 4.2)

Box 1. Post-2015 Global TB Strategy

As 2015 approaches, an evaluation of progress towards the targets for global TB care and control outlined in the Millennium Development Goals, the Global Plan to Stop TB 2011–2015 and other global strategies has illustrated where objectives have been met and where gaps continue to exist. In response to these gaps and in an effort to continue to accelerate progress towards a world free of TB, a strategic framework with the following targets was endorsed at the 66th World Health Assembly in May 2014:

Milestones for 2025 are:
- 75% reduction in TB deaths
- 50% reduction in TB incidence rate.

Targets for 2035 include:
- 95% reduction in TB deaths
- 90% reduction in TB incidence rate.

Achievement of these targets will require integrated patient-centred care and prevention, bold policies and supportive systems, and intensified research and innovation.

Source and notes: Post-2015 Global Strategy and Targets for Tuberculosis Prevention, Care and Control, approved by the World Health Assembly on 19 May 2014; milestones for 2025 and targets for 2035 are relative compared to 2015 figures.

4. Commodity access issues

Although treatment with a 6-month course of first-line TB medicines can cure almost 90 % of TB cases,[3] lack of access to appropriate medicines persists. (7) In 2012, an estimated 3 million people with active TB—over 30 % of all new cases—were not verified as being treated according to WHO recommendations. Commodity access issues, defined here as the gap between those who need treatment and those who receive it, are even more pronounced in MDR-TB and paediatric TB, as described below.

4.1. Commodity access issues related to MDR-TB medicines

Access to MDR-TB medicines is improving—but need for diagnosis still far outstrips demand, with the vast majority of MDR-TB cases never even being diagnosed. In 2012, fewer than one in five MDR-TB cases were appropriately diagnosed and treated. WHO reports that only 83 715 patients of an estimated 450 000[4] total incident cases were diagnosed, and only 77 321 enrolled on second-line treatment. (7) In addition, while 19 % case detection was achieved globally (28 % for pulmonary MDR-TB cases only), variation by region is wide: from 6 % in the Western Pacific, 12 % in the Eastern Mediterranean region and 21 % in South-East Asia, to 42 % in the Americas, 48 % in Africa and 50 % in Europe. Case detection also varies within regions, across countries. (7)

Figure 2 provides an overview of global trends in MDR-TB medicines need, demand and access—where the estimated number of cases is used to illustrate need, number of notified cases is used to illustrate demand, and number of patients enrolled on treatment is used to illustrate access.

Significant progress has been made in enrolling notified cases on treatment, narrowing the gap between demand and access. As recently as 2009, only 65 % of notified MDR-TB cases was enrolled on treatment. By 2010, the market had grown to approximately 45 000 treatment courses (over 80 % of notified MDR–TB cases). (7) In 2012, over 77 000 patients (about 92 % of notified MDR–TB cases) received treatment. Enrolment rates exceeded forecasts for 2012 by over 14 000 cases, but coverage continues to fall short of need and targets—reaching less than half of the goal of enrolling 175 000 patients on treatment by 2012, as established by the Global Plan to Stop TB 2011–2015. (18, 19) Furthermore, many patients do not have access to full drug susceptibility testing (DST): new estimates suggest that less than 20 % of those patients enrolled was treated with the appropriate regimen of second-line drugs. (20) Finally, the complexity, length, cost and poor tolerability of MDR-TB medicines means that, even among those patients who are initiated on treatment, many patients do not complete the full course of therapy.

New developments could help to further narrow this access gap (i.e. those who need treatment versus those who are enrolled on treatment). An innovative diagnostic, the Xpert MTB/RIF assay, is the first of several in the pipeline of emerging new technologies that can diagnose TB quickly and accurately and detect rifampicin resistance in drug-resistant patients. (21) Endorsed by WHO in 2010, with an updated policy related to use released in 2013, the Xpert MTB/RIF assay is now being increasingly adopted worldwide and is increasing demand for MDR-TB drugs. (22) In parallel, the last two years have seen the launch of the first two novel TB medicines in 50 years aimed at MDR TB. (23) Future trends in MDR-TB medicines access are difficult to predict for many market-related reasons, including: fragmentation of procurement; the small base of reliable data and lack of systematic demand forecasting; complexity of treatment; use of new medicines for indications outside of TB and the role of repurposed drugs for MDR TB; and the new developments noted above. However, extrapolation of available data and analysis of directional trends suggests potential for improved access—i.e. increased numbers of patients on treatment.

---

3 If treatment compliance, drug quality, etc. is 100%.

4 Representing 19% of all cases (450 000) and 28% of all pulmonary TB cases (300 000) as reported in the UNITAID Tuberculosis Medicines Technology and Market Landscape, 1st edition, 2013.

Figure 2. Global trends in MDR-TB medicines need, demand and access
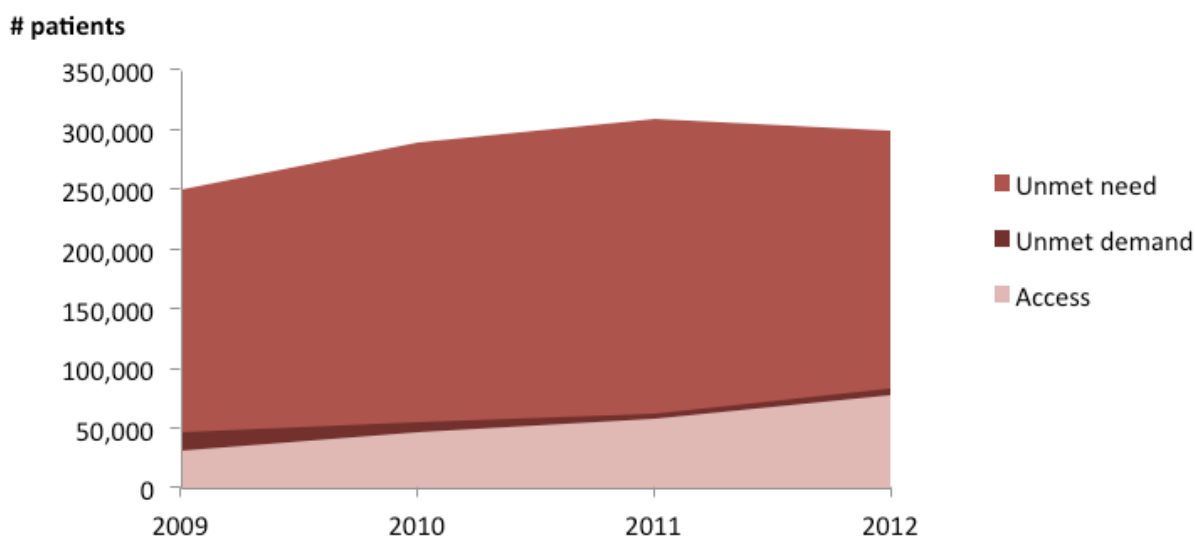
Source and notes: Figures from the WHO Global Tuberculosis Report 2013 (9): need is defined here as the number of estimated cases (among TB patients with pulmonary TB—estimated total cases worldwide in 2012 reported as 450 000); demand, as the number of notified cases; and access, as the number of patients enrolled on treatment.

4.2. Commodity access issues related to paediatric TB medicines

TB continues to be a significant cause of childhood morbidity and mortality globally. WHO estimates that 530 000 cases of TB and approximately 74 000 deaths occurred in (HIV-negative) children under 15 years of age in 2012.[5] Although case reporting has improved in many countries, resulting in 349 000 cases reported to national tuberculosis programmes (NTPs) in 2012 (7), actual figures are likely much higher due to continued challenges in diagnosis, especially for children who are HIV-positive, have other respiratory diseases or suffer from malnutrition (refer to Box 6). Recent estimates suggest the actual number of cases of childhood TB per year is close to 1 million: double the WHO estimate and three times the number of cases reported to NTPs annually. (24-26) In addition, it is estimated that up to 53 million children have a latent infection, representing a substantial reservoir of disease for the future population. (26) Access to TB care is poor: surveys suggest that only half of cases reported to NTPs are treated in some key high-burden countries. (25) Recent studies estimate that GDF supplied approximately 22 % of paediatric formulations needed in the public sector in high-burden countries in 2012 and up to three quarters of notified cases from 2007 to 2012. (27) This suggests that many children receiving treatment are still being treated with drugs of substandard or unknown quality. (28) Even when paediatric TB is diagnosed and treated with QA medicines, there currently remain no appropriate TB medicines in paediatric formulations. Although WHO-prequalified fixed-dose combinations (FDCs) of the four most commonly used first-line medicines exist, none is aligned with current WHO treatment guidelines for children. There continue to be no paediatric guidelines for MDR TB; both dosing recommendations and child-friendly formulations of MDR-TB medicines are needed. Figure 3 illustrates the access gap for paediatric TB medicines, showing attrition from estimated burden through diagnosis and treatment. Progress to date has been limited due to the lack of a market incentive, underestimation of the market size and barriers to market entry. However, efforts to develop appropriate TB medicines for children are now under way—e.g. UNITAID is funding the TB Alliance to speed development of new appropriately dosed, QA, fixed-dose TB medicines for children, with new treatment options expected by 2016.

---

5 Total number of deaths is likely much higher as TB-related deaths in children with HIV are classified as deaths caused by HIV and are not included in the above estimate.

For patients with MDR TB, including children who accounted for a projected 45 000 cases in 2012, (19)[6] current treatment is a combination of injectable and oral drugs with substantial side-effects. The TB pipeline includes new MDR-TB medicines that may be adaptable for children and studies have shown that children given appropriate treatment have had excellent outcomes with clinical cure rates over 80%. (29) For ethical reasons, paediatric trials are generally not started until activity against TB is proven in adults and there is no guarantee that a paediatric indication will be possible for a particular drug (e.g. if adverse event profile in early adult trials precludes use in children). However, with a renewed global focus on childhood TB, there is pressure to decrease the lag time between the initiation of adult and paediatric trials in an effort to get effective, child-friendly TB diagnostics and drugs to market more rapidly. The feasibility of making such products available will also require increased mobilization of human and financial resources, as well as improved collaboration across relevant disciplines, including child and maternal health, nutrition and HIV-related research and services.

Figure 3. Global estimates of paediatric TB medicines need, demand and access
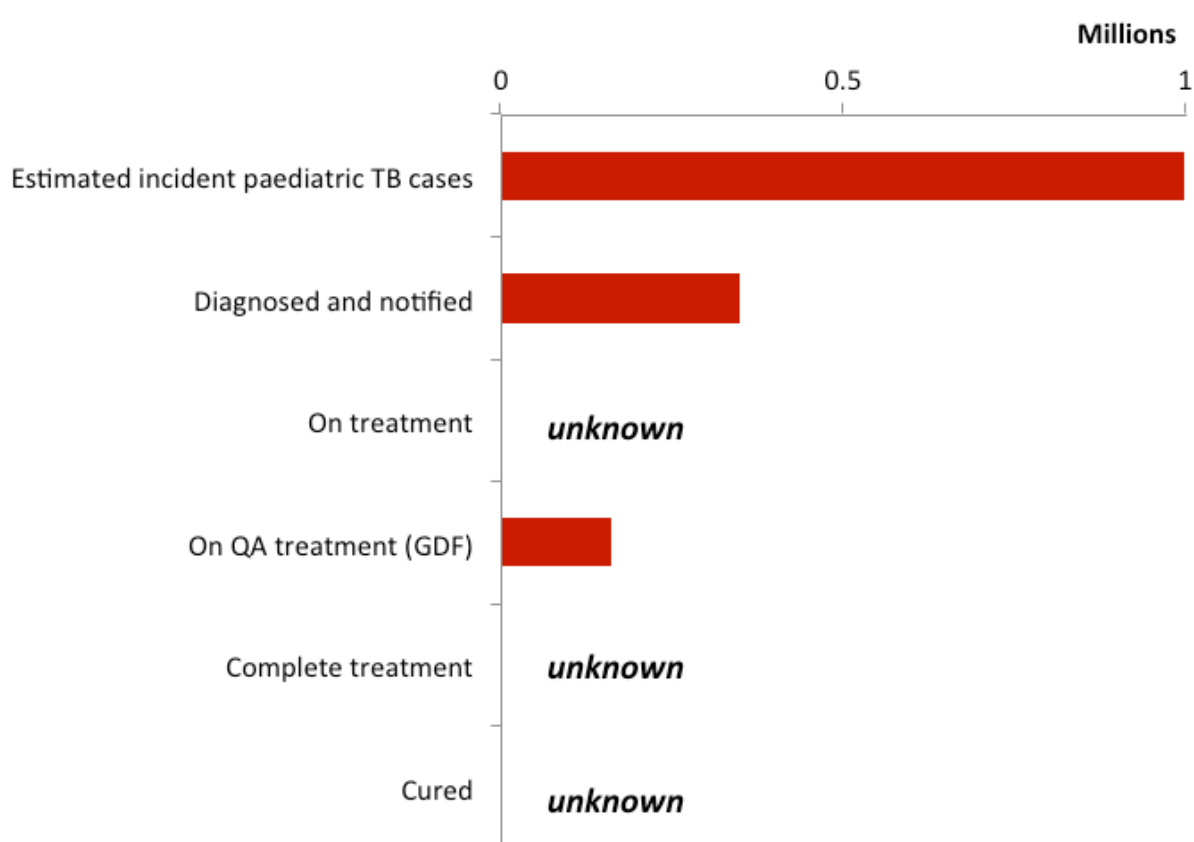
Sources and notes: Figures reflect currently available data, as described in section 4.2 and Appendix 1.

---

6 Crude projections estimate that MDR TB is just as transmissible as DS TB in children, suggesting that children account for 10% of the total burden of TB and MDR TB.

5. Technology landscape

5.1. Technology overview: current available medicines and treatment guidelines

5.1.1. First-line TB medicines and treatment guidelines

First-line treatment regimens for DS TB are standardized, and typically consist of two months of daily isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of daily isoniazid and rifampicin. (30) Two-, three- and four-component FDCs of these drugs are available, as well as injectable streptomycin (used for retreatment patients).

5.1.2. MDR-TB medicines and treatment guidelines

MDR TB, on the other hand, requires treatment for up to two years with complex treatment regimens. Key MDR-TB medicines include:

■ injectables (e.g. amikacin; kanamycin; capreomycin);

■ fluoroquinolones (e.g. moxifloxacin; levofloxacin);

■ oral bacteriostatic second-line agents (e.g. ethionamide; prothionamide; cycloserine; terizidone; para-aminosalicylic acid [PAS]; PAS sodium);

■ agents with limited data on efficacy and/or long-term safety on the treatment of drug-resistant TB (DR TB) (e.g. clofazimine; linezolid; and new drugs: bedaquiline and delamanid).

The 2011 MDR-TB guidance from WHO recommends an intensive phase lasting at least 8 months, and total duration of MDR-TB treatment lasting at least 20 months. (31) In addition, WHO recommends design of a second-line regimen according to the following principles (31):

■ a fluoroquinolone should be used (strong recommendation, very low-quality evidence);

■ a later-generation floroquinolone is preferred to an earlier-generation fluoroquinolone (conditional recommendation, very low-quality evidence);

■ ethionamide (or prothionamide) should be used (strong recommendation, very low-quality evidence);

■ four second-line anti-TB drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase (conditional recommendation, very low-quality evidence);

■ regimens should include at least: pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide) and either cycloserine or PAS (if cycloserine cannot be used) (conditional recommendation, very low-quality evidence).

WHO does not recommend a specific regimen for all patients or geographic areas, but advises national treatment programmes to consider patient-specific factors (e.g. results of DST; previous use of TB medicines and the outcome of that treatment) and overall background resistance in the setting. (31)

Released in 2012, the WHO guidance on the current use of shortened regimens for the treatment of MDR TB recommends that short regimens should be used only as part of research that includes monitoring for at least 12 months after completion of treatment. (32) Additional criteria include: approval of the project by a national ethics committee; following of international standards for trials and safety monitoring (e.g. Good Clinical Practice); and monitoring of the research by a WHO-established independent monitoring board. (33) Current and planned implementation includes both 9-month and 12-month variants, as well as variation in drug choice and duration.

Treatment guidelines for delamanid are currently in development, but in 2013 WHO issued interim guidance on the use of bedaquiline. In addition to strongly recommending the acceleration of Phase III trials to inform future policy on bedaquiline, the guidance noted the following five conditions for its use:

- **Effective treatment and monitoring**: Treatment must be closely monitored for effectiveness and safety, using sound treatment and management protocols approved by relevant national authorities.
- **Proper patient inclusion**: Special caution is required when bedaquiline is used in people aged 65 and over, and in adults living with HIV. Use in pregnant women and children is not advised.
- **Informed consent**: Patients must be fully aware of the potential benefits and harms of the new drug, and give documented informed consent before embarking on treatment.
- **Adherence to WHO recommendations**: All principles on which WHO-recommended MDR-TB treatment regimens are based must be followed, particularly the inclusion of the four effective second-line drugs. In line with general principles of TB therapeutics, bedaquiline alone should not be introduced into a regimen in which the companion drugs are failing to show effectiveness.
- **Active pharmacovigilance and management of adverse events**: Active pharmacovigilance measures must be in place to ensure early detection and proper management of adverse drug reactions and potential interactions with other drugs.

5.1.3. Paediatric TB treatment guidelines

Recognizing the complexities of treating TB in children, WHO released guidance specifically for the treatment of paediatric TB in 2006. (33) This guidance was revised in 2010, and again in 2014, to include:

- significantly higher recommended dosing ranges for isoniazid, rifampicin and pyrazinamide (in response to new evidence on optimal dosing of TB medicines for children) (34)—the 2014 guidelines further adjusted the dosing range of isoniazid from 10–15 mg/kg to 7–15 mg/kg and eliminated maximum doses for pyrazinamide and ethambutol; (35)
- recommendation of a three-drug regimen for the intensive phase of treatment for HIV-negative children; (29)
- removal of streptomycin as a first-line TB medicine due to evidence of increasing resistance and unacceptable side-effects; (34)
- recommendations on treatment of TB and HIV co-infection in children (due to the need for updated guidance on treatment of TB in this important patient group). (34, 36)

Current drugs and recommended doses are shown in Table 3. Currently available FDC products are based on the lower dosing recommendations from previous guidelines. WHO issued guidance indicating how to combine available FDCs to create appropriate doses with the higher dosing ranges. (30) However, the continued use of unmodified FDCs often results in sub-therapeutic doses. (34) Incorrect dosing can lead, in turn, to treatment failure in individual patients and contribute to drug resistance more generally. Treatment guidelines for the treatment of MDR TB in children still do not exist, but are needed.

Table 3: First-line TB medicines, paediatric dosing recommendations

Drug	Dose range (mg/kg)	Maximum dose (mg)
isoniazid	7–15	300
rifampicin	10–20	600
pyrazinamide	30–40	-
ethambutol	15–25	-

Note: In the 2014 WHO revision, the dose range for isoniazid was adjusted to 7–15 mg (from 10–15 mg in 2010) and the maximum doses for pyrazinamide and ethambutol were removed.

Sources: WHO (2010); (34) WHO (2010); (36) WHO (2014). (35)

5.1.4. Isoniazid preventive therapy (IPT) for treatment of LTBI

IPT uses isoniazid to prevent progression of LTBI to an active TB infection. WHO recommends that adults and adolescents living with HIV, with an unknown or positive TB skin test, and who are unlikely to have active TB, should receive daily IPT for at least 6 months and up to 36 months. (37) This includes pregnant women and people on antiretroviral (ARV) therapy, without regard to the degree of immunosuppression. Children older than 12 months who are living with HIV, are unlikely to have TB and have no contact with a person with active TB disease should receive six months of IPT. (10) Among children younger than 12 months of age who are living with HIV, only those with known TB case contact and who are determined to not have active TB should receive six months of IPT. (10) WHO also recommends that all children living with HIV who are treated for TB should receive an additional six months of isoniazid treatment after their TB treatment is completed. (10)

Treatment of LTBI in HIV-negative people is currently not recommended globally, though guidelines are in development. A few countries have independently developed guidelines to treat LTBI to prevent progression to active TB, but these countries tend to have a low TB prevalence. For example, the United States Centers for Disease Control and Prevention (CDC) recommends nine months of isoniazid once-daily—or, in some patients, 12 weeks of isoniazid and rifapentine once-weekly via directly observed therapy. (38) This 12-week regimen has also been demonstrated to be safe and effective in people with HIV. A recent systematic review found that rifampicin- and rifapentine-containing treatment regimens for HIV-negative individuals may be as effective at preventing active TB as IPT, with fewer adverse events. Further research is needed to better understand resistance of and adherence to alternative treatment regimens in low-resource settings. (39)

5.2. Technologies in development and repurposed drugs: TB medicines pipeline and recent updates

As described in section 5.1, TB treatment according to current guidelines can take over two years to complete. Patients must take multiple medicines: the pill burden and potential for drug–drug interactions are high, as shown in Figure 4, and can cause a range of side-effects from mild nausea to potentially irreversible deafness and nerve damage. Efficacy of treatment for MDR TB is particularly poor, with low cure rates. The current scale and pace of the global response to TB achieves only 5% reduction in TB deaths per year. (40) With further development of new technologies, a 20% reduction in TB cases each year is achievable. (40) However, current treatment strategies are insufficient to reduce TB deaths by 95% by 2035, as proposed in the WHO Post-2015 Global Tuberculosis Strategy framework (see Box 1). (13)

A number of significant challenges to TB treatment that require innovative solutions include:

- long duration of treatment for LTBI, DS TB and DR TB;
- low cure rates for DR TB;
- poor tolerability for DR-TB treatment;
- drug–drug interactions among TB medicines, and between TB medicines and ARVs and opioid substitution therapy (OST);
- lack of preventive options for contacts of people with DR TB.

In addition, an estimated US$ 500 million gap in funding for TB medicines research and development has severe consequences: the pipeline for new medicines is scant, with just six novel candidates in clinical development and no candidates in Phase I. Many products in clinical development are progressing slowly, partially due to business decisions or insufficient funding: for example, development of sutezolid stalled when Pfizer exited the anti-infectives market and turned its portfolio over to Sequella.

The following sections detail the challenges as outlined above and in Table 4, and review how repurposed and novel compounds and regimens may begin to be addressed (see Table 5, Table 6 and Table 7). Much of the attention in drug and regimen development focuses on DR TB, due to the urgent unmet need to improve DR-TB therapy and outcomes.

Figure 4. Typical daily pill burden for MDR-TB/HIV co-infected patient >60 kg: 17 tablets, 3 capsules, 2 sachets and 1 intramuscular (IM) injection (excluding ancillary drugs for adverse effects)

Morning dose	Evening dose
pyrazinamide (500 mg): 4 tablets kanamycin (1-g vial): 1 g IM levofloxacin (500 mg): 2 tablets ethionamide (250 mg): 1 tablet cycloserine (250 mg): 1 capsule PAS (4-g sachet): 1 sachet AZT/3TC combination: 1 tablet cotrimoxazole: 1 tablet	ethionamide (250 mg): 2 tablets cycloserine (250 mg): 2 capsules PAS (4-g sachet): 1 sachet pyridoxine (50 mg): 4 tablets AZT/3TC combination: 1 tablet EFV (600 mg): 1 tablet
Total pill burden in morning: 9 tablets, 1 capsule, 1 sachet and 1 IM	Total pill burden in evening: 8 tablets, 2 capsules, 1 sachet.

Source: Reprinted with permission of Partners In Health. Partners In Health (2013). (41)

Table 4. Approaches in development to address challenges with the current standard of care for TB

Challenge	Current standard of care	Approach in development
Long duration of treatment for LTBI	6–36 months of daily isoniazid alone	■ 12 once-weekly doses of isoniazid and rifapentine[2] (42) ■ 1 month daily isoniazid and rifapentine ■ 4 months daily rifampicin[8]
Long duration of treatment for DS TB	6-month regimen	■ 4-month regimens
Long duration of treatment for DR TB	20–24-month regimen	■ 6- to 9-month regimens
Low cure rates for DR TB	50–60% for MDR TB; 11–30% for XDR TB	■ Optimize use of existing medicines via different combinations of more medicines, for shorter treatment times ■ Add new medicines with more potency against MTB
Poor tolerability for DR-TB treatment	Treatment involves multiple adverse effects, painful injections and high pill burden	■ Identify new, safer medicines to replace more toxic or injectable agents and reduce number of medicines in regimen
Drug–drug interactions among TB medicines, and between TB medicines and ARVs and OST	Rifampicin and rifapentine interact with many other TB medicines, with ARVs and with methadone; rifabutin has fewer interactions but is not widely used	■ Create regimens without rifamycins ■ Optimize use of rifabutin ■ Evaluate novel agents' interactions
Lack of preventive options for contacts of people with DR TB	None	■ Levofloxacin-based preventive therapy

2 In the United States, the CDC recommends the use of 12 once-weekly doses of isoniazid and rifapentine, or 4 months daily rifampicin, for certain populations.

Figure 5. Overview of TB medicines pipeline (June 2014)
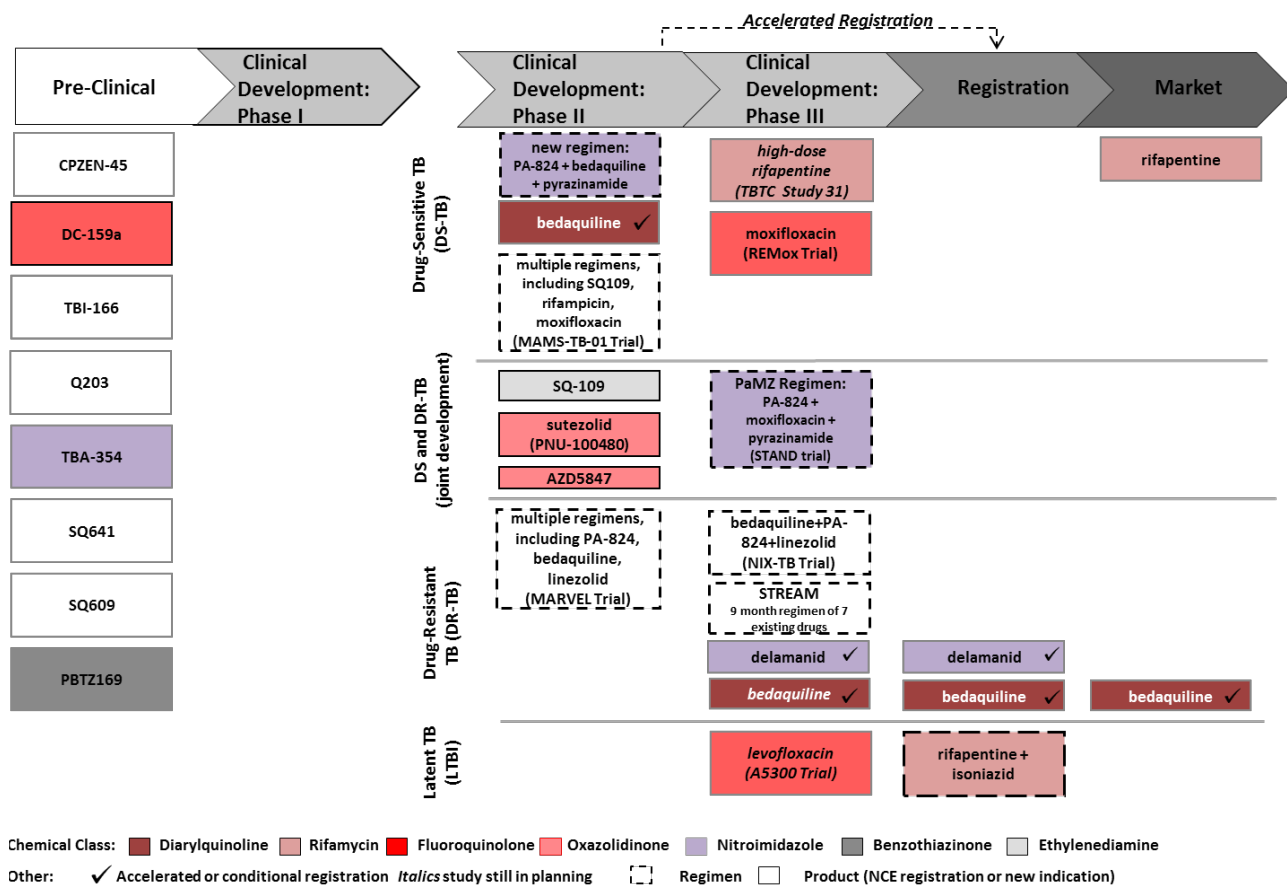
Sources: Adapted by Mengyan Li for UNITAID, from Global TB Drug Pipeline, Working Group on New TB Drugs, and section 5.2 content; with input from Erica Lessem, Treatment Action Group, and Megan Paterson.

Table 5. Repurposed, novel and second-generation medicines by indication and strategies for regimen development

Medicine	LTBI		DS TB	DR TB				Studied as part of novel combination
	Treatment-shortening	Addressing latent MDR TB	Treatment-shortening	Treatment-shortening	Improving efficacy	Improving tolerability		
AZD5847			tbc	tbc	tbc	tbc		
bedaquiline*			✓	✓	✓	✓		✓
clofazimine				✓	✓	✓		✓
delamanid*					✓			
isoniazid				✓	✓	✓		✓
levofloxacin		✓		✓	✓	✓		✓
linezolid				✓	✓			✓
moxifloxacin			✓	✓	✓	✓		✓
PA-824*			✓	✓	✓	✓		✓
rifampicin	✓		✓					✓
rifapentine	✓		✓					
SQ109*				✓	✓	✓		✓
sutezolid			tbc	tbc	tbc	tbc		

tbc: to be confirmed
* Indicates new medicine class.

Note: As sutezolid and AZD5847 have only been in Phase IIa trials and future development plans are not in the public domain, it is unclear what strategies will be pursued in regimen.

Table 6. Existing medicines (approved and unapproved for a TB indication) being repurposed to improve TB treatment (as of May 2014)

Medicine	Class	Phase	Selected trials (sponsors)	Proposed indications	Strategy
clofazimine	riminophenazine	III	STREAM (The Union, USAID, UK MRC)	MDR TB	Treatment-shortening
isoniazid	pyridine	III II	STREAM (The Union, USAID, UK MRC) A5312 (ACTG)	MDR TB	Using higher doses to shorten treatment or to overcome isoniazid resistance in strains with specific mutations
levofloxacin	fluoroquinolone	III II	A5300 (ACTG) A5319 MARVEL (ACTG)	LTBI MDR TB	Treating LTBI in contacts of people with MDR TB; treatment-shortening for MDR TB
linezolid	oxazolidinone	II III	A5319 MARVEL (ACTG) NiX-TB (TB Alliance)	MDR TB XDR TB	Improving efficacy and treatment-shortening
moxifloxacin	fluoroquinolone	III III	REMox (TB Alliance) STAND (TB Alliance)	DS TB DS/DR TB	Treatment-shortening
rifampicin	rifamycin	III III	MAMS-TB-01 (PanACEA, EDCTP) 4R v. 9H (CIHR, McGill University)	DS TB LTBI	Using higher doses to shorten treatment
rifapentine	rifamycin	III	S31 (TBTC) A5279 (ACTG), iAdhere S33 (TBTC)	DS TB LTBI	Using higher doses to shorten treatment

Table 7. Novel and second-generation compounds being developed for TB treatment (as of May 2014)

Medicine	Class	Sponsor	Phase	Proposed indications	Studied as part of novel combination	(Estimated) date of regulatory approval	Recent or anticipated milestone (estimated date)
AZD5847	oxazolidinone	AstraZeneca	IIa	TBA	No	(2025)	Phase IIa study results available (4th quarter, 2014)
bedaquiline*	diarylquinoline	Johnson & Johnson	IIb/ III	DS TB DR TB	Yes (NC001, NC003, NC005, MARVEL, NIX-TB)	(2022) 2012	Phase III study initiated (1st quarter, 2015)
delamanid*	nitroimidazole	Otsuka	III	DR TB	No	2014	Phase III study results available (4th quarter, 2014)
PA-824*	nitroimidazole	TB Alliance	III	DS TB DR TB	Yes (NC001, NC002, NC003, NC005, STAND)	(2019)	Phase III study begins (3rd quarter, 2014)
SQ109*	ethylene diamine	Sequella/ Infectex	IIb/ III	DS TB DR TB	Yes (MAMS-TB-01)	(2022)	SQ109-containing arms discontinued from adaptive Phase IIb study (1st quarter, 2014)
sutezolid	oxazolidinone	Sequella	IIa	DR TB	No	(2025)	Phase IIa study results available (2nd quarter, 2014)

* Indicates new medicine class.

Notes: Sponsors did not provide estimates for estimated regulatory approval of bedaquiline for DS TB, AZD5847, SQ109 or sutezolid. As such, estimates for these medicines/indications were based on the assumptions that candidates poised for Phase IIb require an additional 8 years, and candidates in Phase IIa require 11 years until approval.

5.2.1 Challenge: duration of treatment

Unlike other bacterial infections, TB infection and disease currently take months and sometimes years to treat. For individuals, this long duration makes completing treatment difficult, especially when continuing care can involve missing work, isolation from family and/or months of side-effects. For health-care providers and programmes, the current duration of TB treatment strains financial and human resources, as administering treatment over long periods of time and attempting to ensure follow-up is both costly and time consuming. Shorter treatment timelines could lead to better outcomes by facilitating adherence at the individual level and care delivery at the programme level.

Treatment for DS TB lasts six months and can involve taking multiple pills, which presents a challenge for adherence. Lengthy treatment timelines, coupled with directly observed therapy requirements, also mean that people with TB are forced to choose between attending clinics to receive treatment and attending work to generate income, which creates economic challenges at the individual, family and societal levels. A recent study found that patients spend 77–89% of their average two-month income accessing TB care during the last two months of treatment, and that a 4-month rather than 6-month regimen would significantly reduce indirect costs and out-of-pocket expenses for patients. (43) The problems associated with lengthy TB treatment are further compounded in patients with DR TB, who currently require a higher pill burden and experience more side-effects, and—depending on programmatic requirements—lengthy in-patient hospital stays.

One of the most effective tactics for significantly reducing TB incidence would be to treat LTBI. (44) Affecting an estimated one third of the world's population, people with LTBI also constitute the largest market for TB commodities. Yet, most TB programmes do not even attempt to treat LTBI routinely: many guidelines focus only on treating populations known to have a particularly high risk for disease progression, such as people with HIV and children. Even then, many people with LTBI are not treated, or many initiate treatment with few reaching completion. The lack of both programmatic and individual uptake of LTBI treatment is driven in part by lack of clear guidelines (see section 5.1.4), but also by a lengthy treatment period, which inhibits patient adherence and contributes to continued need for retreatment.[7] Treatment for LTBI can be reduced to just 12 once-weekly doses of isoniazid and rifapentine, but because rifapentine is currently only available in the United States, most countries, if they treat LTBI, rely on 6–36-month regimens of isoniazid alone.

5.2.1.1 In the pipeline: duration of treatment for LTBI

Despite representing the largest market in TB, LTBI receives little attention from the research community. As indicated above, a recent advance came when the CDC Tuberculosis Trials Consortium (TBTC) demonstrated that just 12, once-weekly doses of rifapentine and isoniazid given under directly observed therapy could treat LTBI as safely and effectively as nine months of isoniazid, including in people with HIV. (45) The TBTC is examining in Study 33 whether this regimen can also be administered without directly observed therapy to facilitate programmatic uptake. The United National Institutes of Health (NIH) AIDS Clinical Trials Group (ACTG) Study A5279 is also looking at the potential of rifapentine and isoniazid given daily to shorten treatment to one month in people with HIV. (46) Despite this progress, as noted above, rifapentine poses many market challenges: it is significantly more expensive than isoniazid, despite a dramatic recent 57% price reduction from its sponsor, Sanofi. (47) Furthermore, rifapentine is currently registered only in the United States and as such is not commercially available in settings where TB burden is highest.

Rifampicin, which is cheaper and more widely available, is another alternative to lengthy isoniazid monotherapy for people with LTBI, and is of particular interest after recent isoniazid shortages. The Canadian Institutes of Health Research (CIHR) is funding McGill University's 4R v. 9H study to determine whether four months of rifampicin alone is as safe and effective as nine months of isoniazid, in adults and children.

---

7 Reinfection is a key obstacle to successful uptake of the treatment of LTBI; protection lasts up to three months after treatment completion, but is required again if the patient becomes reinfected, which is common in high-burden countries and is resource-intensive.

5.2.1.2 In the pipeline: duration of treatment for DS TB

Recent strategies to reduce the duration of treatment for DS TB have focused on repurposing fluoroquinolones, raising doses of rifamycins and evaluating new compounds. Current regimens under development could lead to a 4-month treatment course. While certainly an improvement over the six months current standard of care, recent modelling suggested that minimal impact on TB incidence may be expected by reducing treatment time to four months. (48) Additional research, especially identification of more potent compounds, will be necessary to develop shorter regimens, such as those available to treat other bacterial infections like streptococcus and pneumonia in under two weeks.

5.2.1.2a Fluoroquinolones

Fluoroquinolones are currently a backbone of MDR-TB treatment, but, given their potency and tolerability and the paucity of new drug candidates, they are under investigation for their potential to shorten the treatment of DS TB. Results should be available in September 2014 from the TB Alliance REMox trial, which studied two 4-month regimens containing daily moxifloxacin (two months of isoniazid, rifampicin, pyrazinamide and moxifloxacin plus two months of isoniazid, rifampicin and moxifloxacin; or two months of moxifloxacin, rifampicin, pyrazinamide and ethambutol plus two months of moxifloxacin and rifampicin) against the standard 6-month DS-TB regimen (two months of isoniazid, rifampicin, ethambutol and pyrazinamide followed by four months of isoniazid and rifampicin).

The OFLOTUB study had a similar design, attempting to shorten DS-TB treatment by simply replacing an existing drug with a fluoroquinolone (in this case, gatifloxacin). OFLOTUB failed to show that a 4-month gatifloxacin-containing regimen was non-inferior to the standard 6-month DS-TB regimen. Participants in the gatifloxacin arm were 3.8% (95% CI: −0.3% to 8.0%, with non-inferiority bounds set to 6%) more likely to have an unfavorable outcome than those receiving the standard of care. (49) By the time the study results became available in late 2013, the OFLOTUB regimen was obsolete anyway, as gatifloxacin has been withdrawn in many markets due to toxicity. Nonetheless, the results of the study do cast doubt on the ability of replacing a drug in the standard DS-TB regimen with a fluoroquinolone to shorten treatment to four months or less.

The TB Alliance is also pursuing moxifloxacin's potential to shorten treatment for DS TB in combination with new drug PA-824 in their STAND or NC006 trial (announced in April 2014), and the MAMS-TB-01 trial described below includes moxifloxacin in one arm. (50) Previously, price had been a barrier to moxifloxacin use as Bayer held patents in many locations; now, patents are expiring and QA generics are entering the market (refer to section 6.3.3). (51) However, there is debate over use of fluoroquinolones for first-line therapy out of concerns of increased resistance to the class. (52, 53)

5.2.1.2b Rifamycins

Rifampicin is known to be potent against TB, and is widely available from a market perspective. Rifampicin was developed for TB when its active ingredient was expensive; thus, researchers identified an efficacious dose and did not conduct further research to identify a maximum tolerated dose. As such, many TB researchers are now exploring the potential to raise doses of rifampicin to shorten treatment for DS TB (see Tables 5 and 6). The Pan-African Consortium for Evaluation of Antituberculosis Antibiotics (PanACEA), with European & Developing Countries Clinical Trials Partnership (EDCTP) funding, compared doses much higher than the standard 10 mg/kg for bactericidal activity and safety over 14 days, and found that even the highest dose tested of 35 mg/kg was safe, well tolerated and appeared more effective against TB than the standard dose. An extension of this study to examine use of 40 mg/kg of rifampicin for 14 days ended in May 2014; investigators require additional funding to continue testing higher doses of rifampicin (45 mg/kg, 50 mg/kg and 55 mg/kg) to determine a maximum tolerated dose. (54) The same group is testing rifampicin at 20 and 35 mg/kg for longer periods (eight weeks) in the ongoing MAMS-TB-01 adaptive combination study to see if they have potential to shorten treatment. (55)

Rifapentine, even more potent against TB than rifampicin and with a longer half-life, is similarly being explored in higher doses for its ability to shorten treatment after promising results in safety and activity in the TBTC Study 29x. (55) TBTC is planning a 4-month, Phase III Study 31 trial, which will test rifapentine

at a flat dose of 1200 mg in people with and without HIV. As indicated above, market access to rifapentine will require much more widespread registrations and further price reductions.

5.2.1.2c New medicines and combinations

A few of the new medicines and combinations in development are directed towards shortening DS-TB treatment. The previously mentioned MAMS-TB-01 study features an adaptive design to explore the potential of different combinations to shorten DS-TB therapy (see Table 6), two of which included new medicine candidate SQ109 (with and without a higher dose of rifampicin). A preplanned interim analysis eliminated these SQ109-containing arms in March 2014 based on predefined criteria for treatment-shortening potential. While the SQ109-containing arms did not have any safety or inferiority signals, there was no evidence that either was superior to the standard of care in terms of shortening time to negative culture (a surrogate in this study for predicting treatment-shortening capacity). As indicated above, the MAMS-TB-01 trial is continuing with two high-dose rifampicin arms, one of which also contains moxifloxacin.

Based on promising early Phase II data, the TB Alliance is exploring the capacity of regimens containing new medicines PA-824 and bedaquiline to shorten treatment for DS TB. After promising results from the 2-month study NC-002, the TB Alliance announced the launch of the Phase III STAND, or NC-006 trial, in April 2014. STAND will study whether moxifloxacin, pyrazinamide and new candidate PA-824 (at different doses) can reduce treatment to four months; results are anticipated for 2019. (56) Similarly, as the 2-week NC-003 study showed that a combination of bedaquiline, PA-824 and pyrazinamide appeared best at reducing TB bacteria out of several combinations tested, the TB Alliance plans to bring bedaquiline, PA-824 and pyrazinamide into the 2-month NC-005 study. (57) However, there is concern that excess mortality observed in one trial of bedaquiline in people with MDR TB makes it inappropriate for study in people with DS TB, who, despite deserving shorter treatment, do have generally effective and safe treatment. (58) As AZD5847 and sutezolid are in early development, it is still unclear if they will be studied for shorter DS-TB treatment. As the class of oxazolidinones also has mitochondrial toxicity, it is unclear if newer members of this class will have a sufficiently improved safety profile to be considered for DS TB.

5.2.1.3 In the pipeline: duration of treatment for DR TB

The ongoing Phase III STREAM trial was originally designed to determine if a regimen of seven existing drugs (clofazimine, ethambutol, moxifloxacin, pyrazinamide, isoniazid, kanamycin and prothionamide) could be used in combination to shorten treatment to just nine months. This "modified Bangladesh regimen"—so-called because it is based on a previous small operational research study that included gatifloxacin instead of moxifloxacin (59)—is already in use in many settings, including both 9-month and 12-month variants, so its validation via a randomized controlled trial is essential. Enrolment is expected to complete in December 2014. The STREAM study team is now working with Janssen to add two bedaquiline-containing arms into a second stage of the trial. One arm will test whether bedaquiline can replace an injectable to create an all-oral 9-month regimen; the other will examine whether adding bedaquiline can shorten treatment to six months. (43) Programmes and patients alike are eager to adopt shorter regimens, especially ones that focus on widely available existing drugs; however, the numerous medicines involved will only partially address pill burden and tolerability issues.

Several other combination trials are planned or about to launch that hope to further shorten treatment with fewer medicines. The TB Alliance recently launched Phase III STAND trial, noted above, will also include an arm of people with MDR TB with fluoroquinolone and pyrazinamide susceptibility. (60) If successful, this would represent a dramatic reduction to just six months of treatment for people with MDR TB. This regimen is contingent, however, on widespread availability of rapid and accurate DST. NC-005 could also drive a treatment-shortening study if results are promising.

The ACTG MARVEL trial, currently under design, is also looking at various novel combinations that include bedaquiline, PA-824 and pyrazinamide given with either linezolid or levofloxacin in people with MDR TB. ACTG is also exploring the possibility of adding an arm containing delamanid. Similarly, the planned endTB trial, also currently under design, will study novel combinations that include both new and existing TB medicines; refer to Box 4 for further information.

The NiX-TB trial, which is testing six months of bedaquiline, PA-824 and linezolid, could bring a major advance for treatment-shortening of XDR TB—which currently has very lengthy treatment timelines—if found to be effective.

5.2.2 Challenge: poor cure rates for DR TB

Cure rates for MDR TB are typically around 50%. (9) Cure rates for XDR TB can be much lower at 30% or less; a recent study showed that only 11% of patients with XDR TB in a South African cohort study had a favourable outcome after five years of follow-up. (61, 62) Most medicines used to treat DR TB are not validated by clinical trials for TB nor licensed for TB by any stringent regulatory authorities; rather, they are used due to a lack of alternatives and because they have shown activity through clinical practice as opposed to randomized controlled trials. Therefore, much of the data guiding dosing, safety, toxicity and drug–drug interactions are based on anecdotal evidence. The lengthy treatment timelines and poor tolerability for DR TB also contribute to poor cure rates by leading to treatment discontinuation and non-adherence.

5.2.2.1 In the pipeline: poor cure rates for DR TB

The previously mentioned STREAM trial is studying the potential of a modified Bangladesh regimen to shorten treatment for MDR TB. As a non-inferiority trial,[8] it is not designed to demonstrate improved efficacy. However, this regimen could contribute to improved cure rates in practice—for example, if adherence were improved through shorter treatment, even if efficacy were unchanged.

New medicines bedaquiline and delamanid received approval based on their potential to improve the efficacy of MDR-TB treatment. Both approvals were based on Phase II data (meaning that long-term follow-up efficacy data are not yet available) showing that each drug significantly improved the proportion of patients who no longer had TB bacteria in their sputum. A study of bedaquiline found that after six months, 79% of participants taking bedaquiline, in addition to a background regimen, tested negative for TB bacteria in the sputum, versus 58% of patients given placebo with a background regimen, and that those receiving the bedaquiline-containing regimen on average tested negative for TB 42 days earlier than those getting the background regimen and placebo. (63, 64) In a separate study, after two months, 40% of those taking delamanid in addition to a background regimen no longer had TB bacteria in their sputum, versus only 30% of those taking a background regimen with placebo. (65, 66)

These promising early results give hope that these novel agents can improve cure rates for DR TB; however, they require confirmation in larger Phase III trials that monitor longer-term cure rates and TB-free survival. Delamanid's Phase III trial completed enrolment in November 2013; long-term follow-up results are expected to be available in 2017. Bedaquiline, on the other hand, has yet to enter Phase III trials. The STREAM trial plans to add two bedaquiline-containing regimens (one 9-month, injectable-free arm; one 6-month arm with an injectable) in a second stage in January 2015.

The TB Alliance STAND trial will include an arm to look at PA-824, moxifloxacin and pyrazinamide in people with MDR TB. However, conclusions about improvements of cure rates for this regimen will also be challenging as the MDR-TB arm is open-label and will not be compared against a control.

Although AZD5847 and sutezolid are too early in development to determine their potential for improving DR-TB cure rates, it is hoped that they will contribute to more efficacious regimens.

Other trials such as NiX-TB and NC-005 from the TB Alliance, NExT from the South African Medical Research Council, MARVEL from ACTG and endTB from Partners In Health and Médecins sans Frontières are all under development to determine if new medicines can improve outcomes for people with MDR and XDR TB.

---

8 Non-inferiority trials are designed to determine if the effect of a treatment is not considerably worse than the standard of care, or another drug/regimen under study, by a specified margin.

5.2.3 Challenge: poor tolerability for DR TB treatment

All medicines have side-effects, and TB medicines—including first-line medicine—can make patients feel worse than they did before initiating treatment. Tolerating TB medicines is difficult for many patients and can be a barrier to adherence. Tolerability is of particular concern for DR-TB treatment, where the drugs by definition have more difficult safety and tolerability profiles than first-line treatment. These include psychosis (cycloserine), nerve damage (linezolid), deafness (injectables) and QT prolongation, a disturbance in the heart's electrical activity (clofazimine, moxifloxacin). Keeping patients on these medicines for over two years, as required for some DR-TB treatment, can be extremely difficult, painful and dangerous. New, safer treatment options are urgently required.

5.2.3.1 In the pipeline: poor tolerability for DR-TB treatment

New medicines—which are all oral—are currently the most promising option for improving tolerability. Yet, as both delamanid and bedaquiline have only been evaluated as additions to existing multi-drug regimens, their potential to reduce regimens' side-effects by replacing and reducing the number of medicines is still unknown. Both medicines were considered safe and tolerable enough from stringent regulatory authorities to merit approval; but again, Phase III trials and post-marketing surveillance are necessary, especially for bedaquiline, which in one Phase II trial was associated with excess mortality. (64)

PA-824 appears generally safe and well tolerated. (67) AZD5847 and sutezolid are both under examination for their potential to preserve linezolid's efficacy while simultaneously improving tolerability; recent early-stage data indicate that sutezolid is also safe and well tolerated when given for two weeks. (68) Similarly, Partners In Health is currently designing trials to test new and existing drugs for improved tolerability.

5.2.4 Challenge: drug–drug interactions

There are limited data on the drug–drug interactions of most TB medications with treatments for other diseases or conditions, particularly with ART and OST.

Rifampicin was the first medicine in the rifamycin class, which also includes rifabutin and rifapentine. These medicines kill non-replicating persistent organisms not easily accessed by many other medicines. Thus, rifampicin-based regimens are very potent. However, because rifampicin and rifapentine induce the cytochrome p450 liver enzyme, it speeds the metabolism and removal of many other medicines from the body, including certain key ARVs, such as non-nucleoside reverse transcriptase inhibitors and protease inhibitors. The magnitude and duration of rifampicin exposure determines the level of interaction; insufficient concentrations of ARVs are likely to lead to the emergence of drug-resistant HIV.

For some drug users dependent on opioids—a class of drugs that includes heroin, opium, morphine and codeine—medications such as methadone and buprenorphine may be used to help prevent withdrawal symptoms and reduce cravings. However, it appears that rifampicin and rifapentine lower the levels of methadone and buprenorphine in the blood, requiring significant adjustments in the dosages of OST.

Rifabutin has much lower levels of interactions with ARVs and with methadone, and new HIV treatment guidelines recommend rifabutin's use. (69, 70) GDF announced in June 2014 a 58% reduction in the price of QA rifabutin with the introduction of a new manufacturing source. (71)

There are little to no data on interactions between ARVs or OST and other TB medicines, particularly for DR TB.

5.2.4.1 In the pipeline: drug–drug interactions

Research into drug–drug interactions for TB medicines is scant, but consists mostly of dose optimization with the rifamycin class, and a few short studies of new medicines in development.

Bedaquiline interacts with several other drugs. Among TB medicines, rifampicin and rifapentine appear to reduce the amount of bedaquiline in the body by about half; however, this is not clinically relevant as bedaquiline is currently not recommended to be used for the treatment of DS TB. (72) Bedaquiline increas-

es the amount of kanamycin, which is also used for MDR-TB treatment, in the body by about half. (73) Caution should be used with clofazimine, and bedaquiline is generally given with levofloxacin rather than moxifloxacin, due to QT prolongation, although this is not based on clinical outcomes. (74) Small studies have looked at giving a single dose of bedaquiline along with HIV medicines, and found that efavirenz appears to reduce the amount of bedaquiline in the body by about half over time, that lopinavir/ritonavir slightly raises the amount of bedaquiline in the body (long-term modelling is needed), that bedaquiline and nevirapine do not interact, and that ketoconazole and bedaquiline should not be taken together for more than two weeks at a time unless potential benefits outweigh risks, as ketoconazole increases the amount of bedaquiline in the body and both cause QT prolongation. (64, 73, 75)

Delamanid appears to have few drug–drug interactions with HIV and other medicines; a Phase I study conducting a pharmacokinetic evaluation over 14 days in healthy subjects found that delamanid did not affect tenofovir or lopinavir/ritonavir drug exposure. Tenofovir had no effect on delamanid exposure, while lopinavir/ritonavir increased exposure to delamanid by 20%. (76) No data exist as to whether delamanid is safe to use with other QT-prolonging TB drugs (including bedaquiline, clofazimine and moxifloxacin), though the ACTG 5343 study will examine delamanid and bedaquiline's safety together, with a target start date of January 2015; results are expected in early 2017.

PA-824 is not expected to have many drug–drug interactions based on its chemical properties. A Phase I study found that lopinavir/ritonavir reduces exposure to PA-824 slightly, efavirenz reduces exposures of PA-824 about 30%, and rifampicin reduces exposure to PA-824 significantly. (73, 77) Required dosing adjustments as a result of the trial, if any, cannot be determined until the target dose of PA-824 to achieve optimal effect is known.

5.2.5 Challenge: lack of preventive options for contacts of people with DR TB

While treatment options for people with LTBI are lengthy, validated preventive options for contacts of people with MDR TB do not exist. Potentially millions of people have LTBI due to contact with people with MDR TB. As their infection would be, by definition, resistant to isoniazid and rifamycins, they lack options for treating their infection to prevent it from developing into active disease.[9]

5.2.5.1 In the pipeline: preventive options for contacts of people with DR TB

A recent observational study based on a 2008 outbreak of MDR TB in Micronesia indicated that treating contacts of people with MDR TB with a fluoroquinolone and ethambutol or ethionamide was feasible and potentially useful. (73) The NIH and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) networks are now working together to plan the study A5300 of levofloxacin-based preventive therapy for contacts of people with MDR TB. If effective, this study would provide long-awaited data to guide the prevention of MDR TB.

---

9 Two additional observational studies are currently looking at preventive options for children who are contacts of people with DR TB: Seddon JA et al. Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study. Clin Infect Dis. December 2013;57(12):1676–84. doi: 10.1093/cid/cit655; Adler-Shohet FC et al. Management of latent tuberculosis infection in child contacts of multidrug-resistant tuberculosis. Ped Infect Dis J. (e-pub ahead of print). doi:10.1097/INF.0000000000000260.

6. Market landscape

6.1. Market overview

Volume estimates

The burden of TB and available epidemiological estimates (section 3) are often poor indicators of market size, due to significant gaps in access to commodities (section 4). For example, in 2012, of an estimated 8.6 million new cases of TB, as many as 3 million were not diagnosed, notified to national TB control programmes and reported to WHO. (9) Access to appropriate diagnostics and TB medicines is significantly lower in people with MDR TB: only 19% of MDR-TB cases was diagnosed and notified in 2012, and even fewer received appropriate treatment. (9) Similarly, TB in children is significantly underdiagnosed and undertreated. Although reporting is incomplete, WHO estimates that of 530 000 cases of paediatric TB in 2012, only 349 000 were notified. (9) Poorly adapted diagnostics mean that many cases of TB in children go undetected: recent estimates suggest that close to 1 million children likely need treatment for TB each year. (24, 78) In addition, no appropriately dosed, QA, paediatric formulations of TB medicines exist that are aligned with the current WHO recommendations, so even those children who do receive treatment often take TB medicines intended for adults (e.g. split or crushed tablets). (25, 79)

The total volume of the TB medicines market in 2012 (public sector only), based on reporting to WHO (9), comprised approximately:

■ 5.7 million courses of first-line treatment of TB in adults;[10, 11]
■ 77 000 courses of treatment for MDR TB in adults.

These estimates exclude the private sector, for which volume data are incomplete. However, in some high-burden countries, the volume of first-line TB medicines sold in the private sector can exceed the amount needed to treat all incident TB patients with a full treatment course. This may reflect overly long treatment, repeated treatments of inappropriate length and inappropriate treatment of other respiratory conditions with TB drugs. (80)

Apart from some isolated paediatric-specific formulations, data do not indicate whether particular formulations are used to treat adults or children. Therefore, these estimates cannot be used to determine paediatric TB treatment coverage in the private sector. For the public sector, GDF procured over 175 000 courses of paediatric TB treatment in 2013 with donor funding (81) (187 996 and 162 000 courses in 2011 and 2012, respectively). (82) However, this procurement mechanism is thought to reach only one in five children estimated to have TB. The remainder are either untreated, or treated with adult medicines (e.g. crushed or split tablets) or paediatric dosages of unknown quality. (25)

Value estimates—and the issue of market fragmentation

By 2015, a total of US$ 8 billion per year will be needed for the TB response in low- and middle-income countries, including over US$ 5 billion to detect and treat DS TB, and about US$ 1.6 billion for treatment of MDR TB. While domestic funding for TB care is sizeable (US$ 5.3 billion in 2013), an additional US$ 1.6–2.3 billion in annual donor funding is still required to address gaps. (9) Currently expected to reach US$ 0.8 billion in 2013, international donor funding for TB is still significantly less than that for malaria (US$ 1.9 billion in 2012) (83) or HIV (US$ 7.9 billion in 2012). (84)

---

10 Based on global case detection rate reported in the WHO Global Tuberculosis Report 2013: an approximate indication of the proportion of all incident TB cases that are diagnosed, reported to national treatment programmes and started on treatment.

11 The UNITAID 2012 Tuberculosis Medicines Technology and Market Landscape reported 6.2 million courses of first-line treatment in adults derived from the number of notified cases in 2011; the 2012 value is derived from the case detection rate and thus does not reflect a decrease in the size of the market, but a difference in methodology. If using case detection rate with the 2011 data, then the volume of the first-line market would have been estimated at 5.7 million courses of treatment (i.e. stable from 2011–2012).

The total value of the TB medicines market in 2012 (public and private sectors), based on a model created by UNITAID, is estimated to be approximately US$ 700 million, including:

- US$ 425 million for first-line treatment of TB in adults;
- US$ 300 million for treatment of MDR TB in adults.

Value estimates are uncertain, given the significant but poorly characterized role of the private sector in procuring TB medicines—particularly MDR-TB medicines, which are procured in a wide range of complex regimens. As before, this estimate does not include treatments for TB in children, due to lack of data. While GDF procured over 175 000 paediatric TB treatments in 2013 (82), the total market is uncertain. If up to 1 million children need TB treatment annually (24), however, and assuming an average first-line regimen costs roughly US$ 30, then the potential market for paediatric TB medicines could be up to US$ 30 million. With these assumptions, but only 349 000 cases of paediatric TB reported to NTPs **in 2012 (9)**, **the actual value of all paediatric TB medicines was probably approximately US$ 10 million**.

There is **no single dominant purchaser** of TB medicines. Instead, the **market is fragmented** across donors, countries' own programmes (i.e. public non-donor, or government, purchases) and the private sector. As described above, GDF supplies QA TB medicines for both the donor-funded segment (i.e. for countries included in donor grants) and provides direct procurement for countries. GDF not only represents an important mechanism for supply of TB medicines (e.g. linking country needs with suppliers and enabling price reduction), but also provides technical assistance, supply chain management and other services. Nevertheless, GDF is one of many critical stakeholders that buy TB medicines. (85) Indeed, in 2010, 13 of 22 high-burden countries reported procuring domestically manufactured first-line TB medicines. (86)

Provision of TB medicines in the private sector is thought to be significant, especially in high-burden countries such as India, Indonesia, Pakistan and the Philippines (and China, in terms of absolute number of patients) (80)—recent estimates suggest over half of all patients in many countries initially seek care in the private sector. (87) **However, visibility on the private-sector market segment is poor**: private-sector market size, treatment patterns and other dynamics have been examined in 10 high-burden countries representing 60% of the global burden of TB, but this information is lacking for most low-income countries. Although the PPM approach aims to align private-sector care with national treatment programme standards, the role of PPM providers is thought to be limited in many countries (80), contributing an estimated 10–40% of global case-finding and significantly less to treatment (since so many PPM providers refer to the public sector for treatment). (4) Figure 6 and Figure 7 show the estimated value of the global markets for TB and MDR-TB medicines in 2012 (unless specified otherwise), based on the best available data, with a breakdown by procurement channel.

Figure 6. Value of the 2012 first-line TB medicines market, by procurement channel (US$ millions)
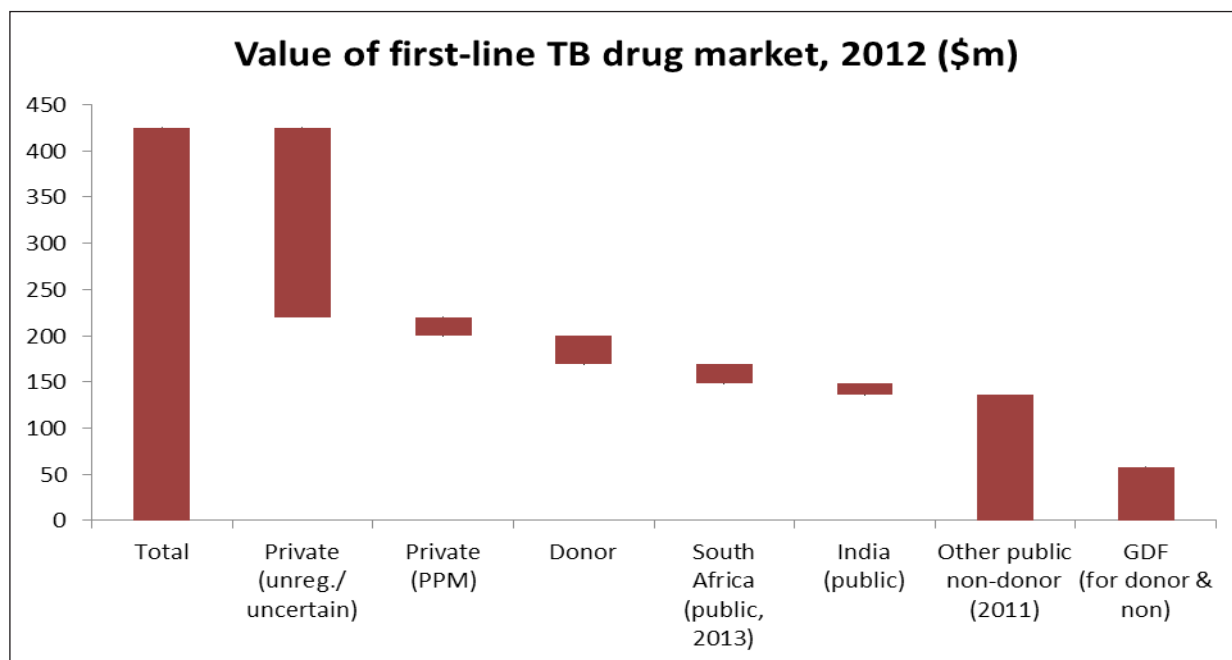
Note: Total market approximated from build-up of various procurement channels, as described in Appendix 1.

Figure 7. Value of the 2012 MDR-TB medicines market, by procurement channel (US$ millions)
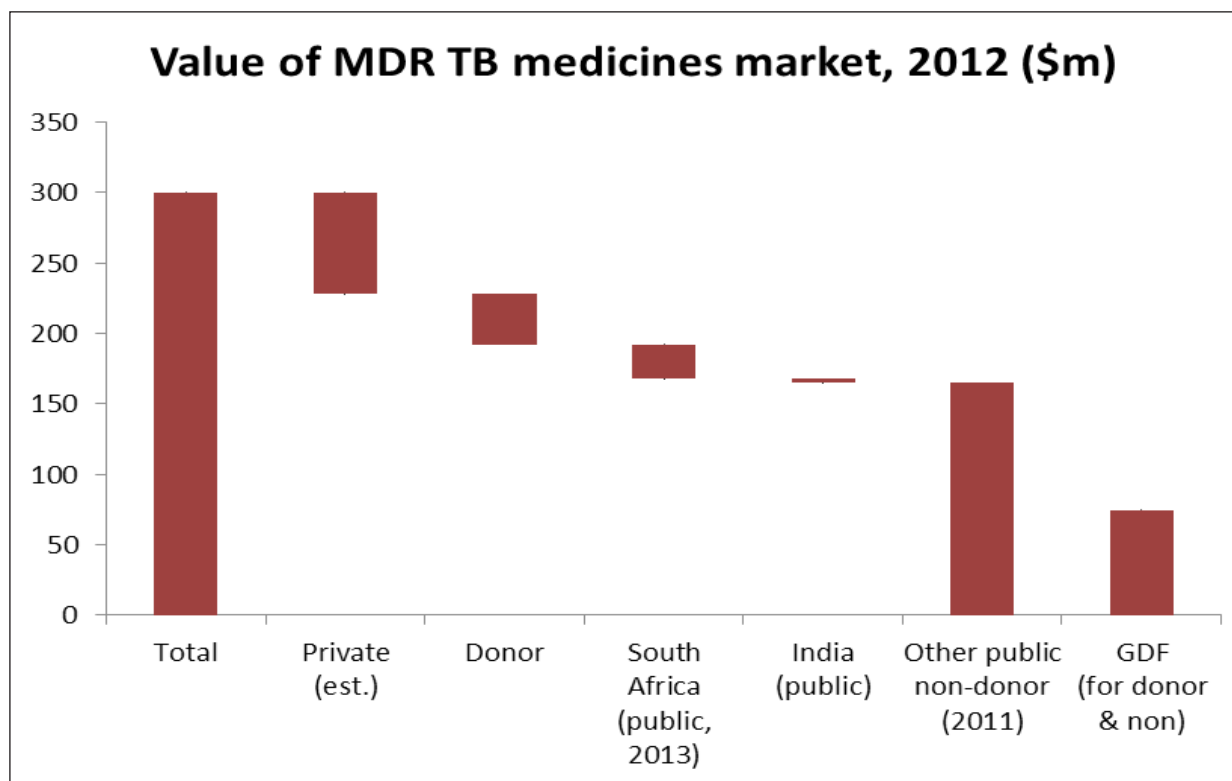
Notes: Total market approximated from build-up of various procurement channels, as described in Appendix 1.

Each purchaser of TB medicines can have unique procurement and quality requirements (Box 2). Furthermore, as shown in Figure 8, many regimens can be used to treat TB (particularly MDR TB)—with each regimen comprising potentially interchangeable medicines and/or formulations (e.g. dosage forms or packaging options). This variation effectively fragments already small TB medicines markets, in turn reducing the commercial incentive for manufacturers to participate (e.g. lower total market size, limited potential for economies of scale), and increasing the complexity of operations for those that do engage (e.g. forecasting, supply chain management).

Figure 8. Number of possible MDR-TB regimens that can be designed from most commonly used MDR-TB drugs

SOURCE: World Health Organization (2011) Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization
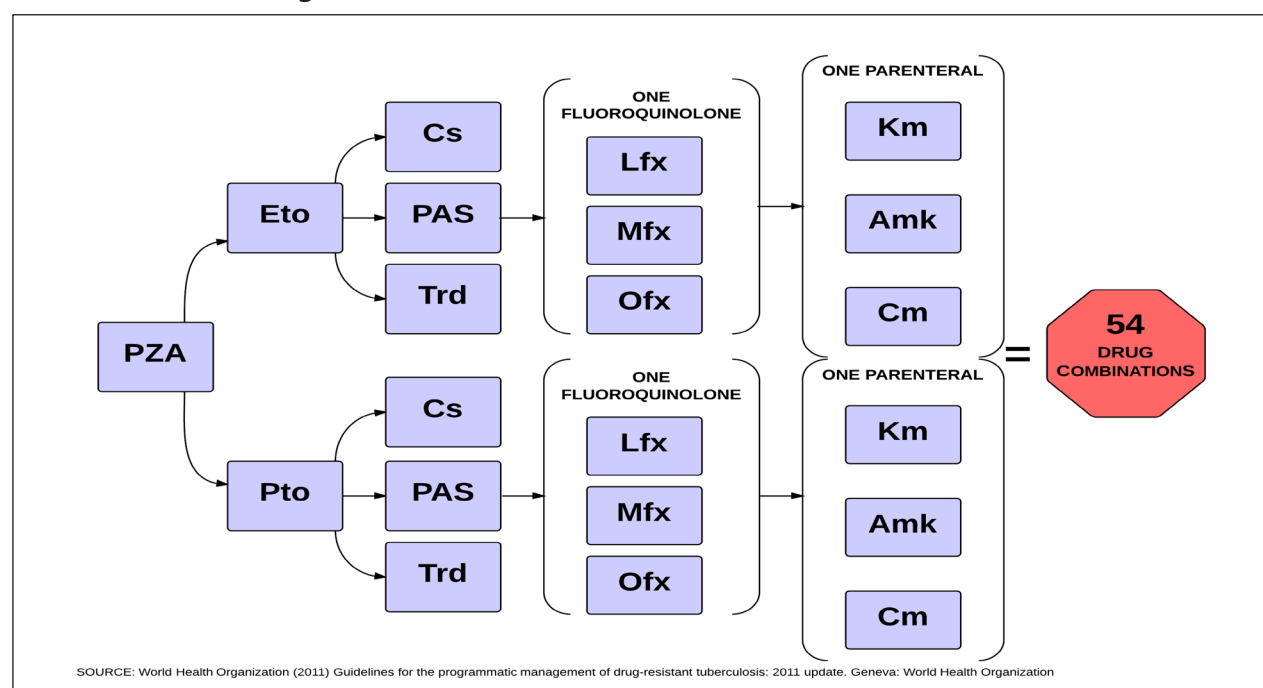
Notes: Amk: amikacin; Cm: capreomycin; Cs: cycloserine; Eto: ethambutol; Km: kanamycin; Lfx: levofloxacin; Mfx: moxifloxacin; Ofx: ofloxacin; PAS: para-aminosalicylic acid; Pto: prothionamide; PZA: pyrazinamide; Trd: terizidone.

Sources: Partners In Health; Médecins sans Frontières; Interactive Research and Development; graphical interpretation of WHO (2011). (31) Reprinted with permission of Partners In Health.

An overview of donor-funded purchases of TB medicines illustrates the market effects of the resulting fragmentation on a relatively small TB medicines market (refer to Figure 9). When these donor-funded purchases are considered alongside estimates of purchases by non-donor stakeholders, as shown in Figure 10, the limited leverage of donors to influence the TB medicines market is particularly evident. However, it should be noted that due to differences in quality or other requirements, donor- and non-donor-funded TB medicines markets are sometimes discrete, with little overlap between suppliers. While this reduces volumes, it also increases the relative leverage (e.g. of GDF) with specific manufacturers participating in each segment.

While there may be scope for simplifying treatment, some of the variation in TB medicines is clinically necessary. As noted in the UNITAID 2013 Tuberculosis Market Forum (Box 3), further evidence is needed to understand where streamlining may be possible, thus helping to stabilize TB medicines markets.

It should also be noted that while consolidation of regimens could improve market dynamics, new longer-term challenges could result. The market for MDR-TB medicines is small relative to other therapy areas, and in spite of potential for growth (e.g. if all estimated cases were diagnosed and enrolled on treatment), it will remain a modest market opportunity for manufacturers. Even fewer manufacturers may be required to sustain a more focused market comprising shorter regimens. Market interventions will, therefore, require continued coordination across partners and initiatives, particularly as the market evolves as a result of these interventions.

Box 2. Quality assurance of TB medicines

Quality of medicines can be regulated by bodies including national drug regulatory authorities or the WHO Prequalification of Medicines Programme (WHO PQ). Requirements for registration can vary by regulator (and by type of registration), but may include documentation supporting claims for the product chemistry, manufacturing, control, performance, etc. Product testing, such as quality control or performance testing and/or manufacturing site inspections or audits, may also be required.

Quality requirements for TB medicines also can be specific to procurer. Many donors, including UNITAID and the Global Fund, typically require that medicines procured with their funds be approved by WHO PQ or a stringent regulatory authority, such as the US FDA or the European Medicines Agency (EMA).[1] In the absence of both WHO PQ and stringent regulatory authority approval, the Global Fund can convene an Expert Review Panel (ERP) to assess quality assurance.[2] (88) Reflecting efforts to harmonize quality requirements, GDF procures only QA medicines—e.g. approved by WHO PQ, a stringent regulatory authority or ERP. Despite these requirements, QA MDR-TB medicines are thought to make up only 13% of the total market. (89) National governments procuring medicines often require local regulatory approval, for which requirements and stringency vary by country. Manufacturers considering supplying TB medicines to multiple countries face many inconsistent registration and quality assurance processes that can deter manufacturer engagement given the small market potential. As a result, TB medicines purchased through the private sector are often of variable or unknown quality. For example, a WHO survey of the countries of the former Soviet Union found that over one quarter (28.3%) of products containing rifampicin in the private and public sectors did not meet quality specifications;[3] predominantly due to an unacceptably low level of active ingredient. (90) A more recent study of isoniazid and rifampicin solely in the private sector found that over 9% of TB drugs was of substandard quality overall (16.6% across several African cities, 10.1% in Indian cities and 3.9% in cities in other middle-income countries).[4] (91) Achieving the highest quality standards is both time and resource intensive, requiring ongoing quality assurance staffing support, therefore, financial incentives must be present for existing manufacturers to raise their quality standards or for new manufacturers to enter the market.

In summary, variation in quality requirements can fragment TB medicines markets, in addition to potentially compromising patient safety and perpetuating the spread of TB through use of drugs of questionable quality. Furthermore, an insufficient number of QA versions can concentrate supplier power, limit competition and increase prices.

---

1 The Global Fund defines a stringent regulatory authority as: (a) a member of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH); or (b) an ICH Observer – European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and WHO; or (c) a regulatory authority associated with an ICH member through legally binding mutual recognition, including Australia, Norway, Iceland and Liechtenstein.

2 If ERP deems a product acceptable, it can be procured with Global Fund monies for up to one year, provided the manufacturer submits an application to WHO PQ for consideration.

3 Results also highlighted that none of the medicines tested from GDF had any quality deviations.

4 African cities studied: Luanda, Angola; Lubumbashi, Democratic Republic of the Congo; Cairo, Egypt; Addis Ababa, Ethiopia; Accra, Ghana; Nairobi, Kenya; Lagos, Nigeria; Kigali, Rwanda; Dar es Salaam, United Republic of Tanzania; Kampala, Uganda; Lusaka, Zambia. Indian cities studied: Chennai, Delhi, Kolkata. Middle-income country cities studied: Bangkok, Thailand; Beijing, China; Istanbul, Turkey; Moscow, Russian Federation; Sao Paulo, Brazil.

Figure 9. Donor-funded purchases of medicines to treat HIV/AIDS, malaria and TB by product formulation and pack size, 2012 (US$ millions)
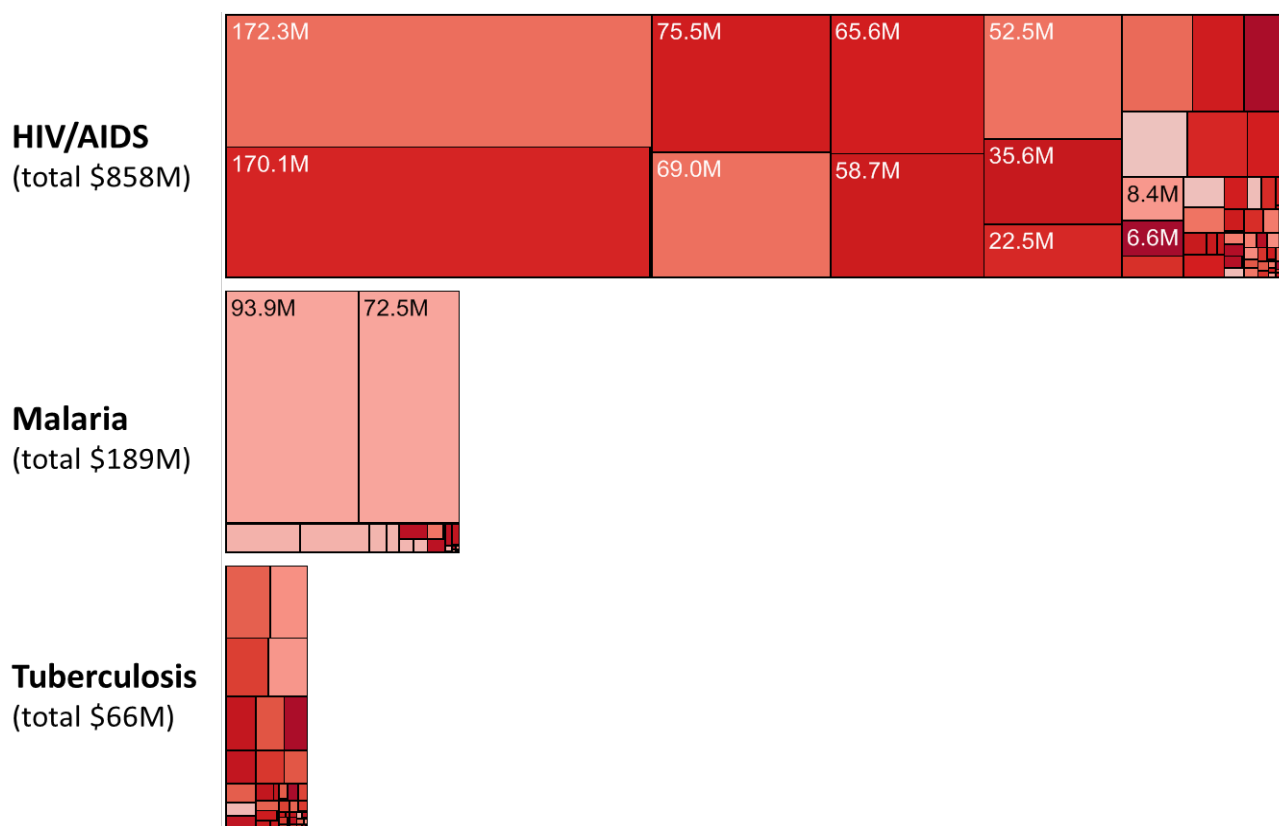
Notes: The size of each box is proportional to donor-funded purchases of medicines split by product formulation and pack size.

Sources: Donor-funded medicines purchase transactions from the PQR, the Global Fund Voluntary Pooled Procurement Programme, the United States President's Emergency Plan for AIDS Relief as provided by the Supply Chain Management Systems, UNITAID as provided by the Clinton Health Access Initiative and UNICEF, and the Affordable Medicines Facility: Malaria. Image credit: Patrick Aylward for UNITAID.

Figure 10. Total estimated purchases of medicines to treat HIV/AIDS and TB by product formulation and pack size, 2012 (US$ millions)
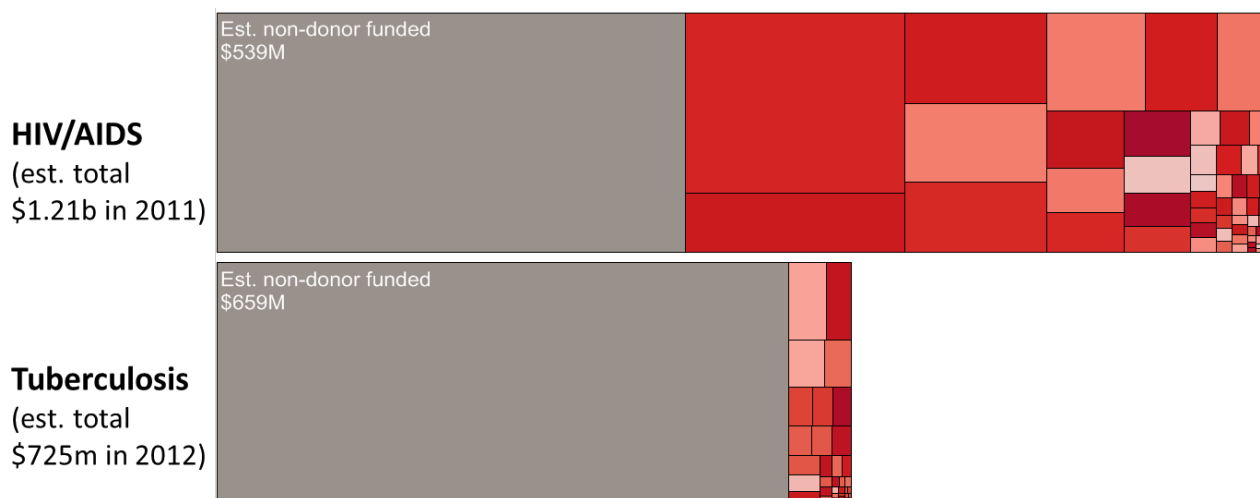
Sources: 2012 donor-funded medicines purchase transactions from the PQR, the Global Fund Voluntary Pooled Procurement Programme, the United States President's Emergency Plan for AIDS Relief as provided by the Supply Chain Management Systems, UNITAID as provided by the Clinton Health Access Initiative and UNICEF, and the Affordable Medicines Facility: Malaria. Total market estimate (HIV, 2011): Clinton Health Access Initiative: The State of the Antiretroviral Drug Market in Low- and Middle-Income Countries. November 2013. Total market estimate (TB, 2012): as above. Image credit: Patrick Aylward for UNITAID.

Box 3. UNITAID 2013 Tuberculosis Market Forum

2013 marked the inaugural UNITAID Tuberculosis Market Forum, a platform to facilitate open exchange of ideas on TB commodity market needs and opportunities. Co-hosted with USAID in 2013, the Tuberculosis Market Forum examined shortcomings and opportunities for market-based intervention. Key outcomes focused on the need to support simpler TB treatment, better forecasting and procurement, optimized production of TB medicines and APIs, and stakeholder coordination.

Outcomes in brief

Simplified TB treatment could foster healthier markets. Over 50 regimens can be used to treat MDR TB, fragmenting an already small market and reducing incentives to manufacture. While complexity could be reduced, some variation is clinically necessary. More evidence is, therefore, needed to streamline treatment options. Work to generate clinical data could help focus the market and inform the optimal use of new tools.

Better forecasting and procurement could alleviate TB medicine shortages. The small and fragmented MDR-TB medicines market is particularly affected, with access to QA drugs under continuing threat. Supply disruptions are a symptom of low and variable demand, unreliable projections and few suppliers. More accurate forecasts improve supplier confidence and production planning and assures timely payment. Other mechanisms—such as strategic stockpiles of key medicines—can also help stabilize supply.

Optimized production of TB API and finished product could promote better access to appropriate commodities. Currently, production inefficiencies and near monopolies for some products lead to high prices and supply disruptions. Approaches to stabilize production or competitiveness may include technical assistance or incentives such as advanced market commitments. However, each market segment can have different economic considerations. For example, production of some APIs is low margin and sensitive to economies of scale, while some finished product markets are more competitive. Market interventions may need to target a different balance of competition and consolidation for each segment. Correct timing of interventions is also critical, since work in one area impacts market dynamics in another.

Harmonized approaches to TB care across public, private, and donor-funded segments could improve market dynamics and public health outcomes in TB. Markets for TB medicines are complex and fragmented: people with TB often seek care in the private sector, while governments also buy TB medicines and diagnostics. Donors are left with small market shares and limited leverage and limited visibility to influence global TB markets. More strategic coordination among all purchasers of TB commodities—including through innovative new business models—could help define and improve global TB markets.

Sources: Adapted from the UNITAID 2013 Tuberculosis Market Forum discussion paper, prepared by Jennifer Cohn and Maarten van Cleeff with support from UNITAID and USAID.

Box 4. Addressing the evidence gap to increase access to new MDR-TB medicines and reduce market fragmentation: expand new drug markets for TB (endTB)

Many treatment options and a limited evidence base contribute to fragmentation of MDR-TB medicines markets. Already small markets are reduced further, decreasing incentives for manufacturers to enter or stay in the market. The 2013 Tuberculosis Market Forum (refer to Box 3) highlighted the potential for market-based interventions to generate evidence for priority treatment options and reduce "non-essential" variation (i.e. unlinked to clinical need). If new, evidence-based regimens eventually replace current WHO standard therapy for MDR TB, significant market consolidation could occur.

In May 2014, UNITAID committed US$ 60 million to endTB, a project designed to radically change the MDR-TB medicines market. Through this initiative, consortium partners Médecins sans Frontières, Partners In Health and Interactive Research & Development will foster early adoption of new TB drugs and regimens in a manner that generates evidence on safety and efficacy, leading to simplified treatment regimens and consolidated demand, as illustrated in Figure 11.

The project is designed to drive new TB drugs into countries and find a better MDR-TB treatment regimen. Activities in 17 countries aim to accelerate access to new MDR-TB treatments, including new drugs bedaquiline and delamanid, and a clinical trial to devise a simpler, safer, more effective treatment regimen targets an increase in cure rate from 48% to 70% and a nearly 10-fold increase in the number of cases averted.

Figure 11. The potential of endTB evidence-generation to consolidate the MDR-TB medicines market

Numerous non-standard regimens and different regimens for MDR-TB, pre-XDR-TB and XDR-TB, composed of 22 different drugs

isoniazid (high-dose)
ethambutol
pyrazinamide
kanamycin (injection)
capreomycin (injection)
amikacin (injection)
moxifloxacin
levofloxacin
ofloxacin
gatifloxacin
ethionamide
prothionamide
cycloserine
terizidone
PAS
PAS sodium
linezolid
clofazimine
amoxicillin/clavulanate
meropenem
imipenem/cilastatin
clarithromycin

Possible priority TB drugs for END-TB regimen development (7-9 different drugs)

delamanid
bedaquiline
moxifloxacin
linezolid
clofazimine
pyrazinamide
additional tbc

1-3 priority regimens including new TB drugs that treat all forms of MDR-TB including pre-XDR-TB and XDR-TB

5-8 priority TB drugs to treat MDR-TB

Sources: Partners In Health; Médecins sans Frontières; Interactive Research and Development. Graphic reprinted with permission of Partners In Health.

6.2. Market for first-line TB medicines to treat DS TB

6.2.1. Introduction

First-line medicines to treat DS TB constitute the largest market segment by volume and value—a segment that is relatively stable and characterized by mostly generic, low-cost products. Approximately 6 million first-line TB treatment courses are required for treatment delivered through the public sector alone.[12] As shown in Figure 6, the global market for first-line TB medicines is estimated to be approxi-

---

12 Based on global case detection rate reported in the WHO Global Tuberculosis Report 2013: an approximate indication of the proportion of all incident TB cases that are diagnosed, reported to national treatment programmes and started on treatment.

mately US$ 425 million, a figure that has remained relatively stable since 2009. First-line TB medicines include isoniazid, rifampicin, pyrazinamide and ethambutol; two-, three- and four-component FDCs of these drugs; and injectable streptomycin (used for retreatment patients). A standard regimen of QA first-line treatment, comprising two months of daily isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of daily isoniazid and rifampicin, costs roughly US$ 22 per patient. (9, 89)

6.2.2. Buyers of first-line TB medicines

National governments play a significant role in funding TB care and control, including procurement and provision of first-line TB medicines through national treatment programmes (Figure 6). Indeed, a 2013 publication on the role of GDF suggests that changes in market share may reflect increased provision of first-line TB medicines by national governments' own public-sector programmes. (85) However, there is wide variation in levels of domestic funding. In Brazil, the Russian Federation, South Africa and China, nearly all (~ 95 %) funding for TB care and control is from domestic sources. (9)[13] Outside Brazil, Russian Federation, India, China and South Africa (BRICS), countries are often highly dependent on external funding sources. Some countries have transitioned from donor dependence to domestic funding for first-line TB medicines (6), but **in many low-income countries, donor funding remains crucial for providing basic TB care, including procurement of first-line TB medicines**. In the 17 high-burden countries excluding BRICS, donor funding accounted for 35 % of total funding in 2013. In Afghanistan, Pakistan, the Democratic Republic of the Congo and Uganda—high-burden countries that are also low-income—over 80 % of TB funding was supplied by donors in 2013. (9)

Overall, procurement of public- and donor-funded first-line TB medicines is estimated to be approximately US$ 200 million, or nearly half of the total market in 2012 (Figure 6). Of this, over 80 % (US$ 169 million) reflects public (non-donor-funded) first-line TB medicines procurement. For example, the South African government plans to spend about US$ 41 million, on at least 1.5 million first-line TB treatment courses, over two years.[14] (2, 3) Indian government purchases include over 1 million first-line TB treatment courses in one year.[15] (5) Analysis of PQR data shows Global Fund procurement of first-line TB medicines worth US$ 27 million in 2012. With the Global Fund responsible for 88 % of all donor funding (1), this suggests donor-funded procurement of first-line TB medicines totalled at least US$ 31 million in 2012.

GDF reported 2012 procurement of first-line TB medicines worth approximately US$ 58 million. (92) A 2013 publication estimated that this procurement, for both donor-funded and public non-donor segments, accounts for 35.4 % of all reported TB cases, or 24.4 % of estimated cases. (85) Further analysis of GDF's evolving role in procuring TB medicines has been conducted, with publications forthcoming.

Despite the importance of procurement funded by national governments and donors, **many patients with TB access first-line medicines in the private sector**, a market segment that is poorly characterized, but estimated to be worth nearly US$ 230 million in 2012 (Figure 6). In the private sector, lack of regulation often results in care that is not aligned with WHO recommendations, and TB medicines purchased in the private sector are often of variable or unknown quality. For example, a study of first-line TB medicines isoniazid and rifampicin showed that over 9 % of all private-sector TB drugs tested was of substandard quality (refer to Box 2 for further detail). (91) In addition, out-of-pocket payments mean that patients accessing care in the private sector often do not complete a full course of treatment, resulting in suboptimal health outcomes and increased risk of drug resistance. PPM approaches, intended to standardize and align private-sector care with national treatment programme standards, are still limited in scope in many countries, accounting for only a fraction of the estimated private market for first-line TB medicines (Figure 6). (86) More work is needed to improve visibility on private-sector market dynamics, particularly in the unregulated private segment.

---

13 Funding for overall TB care and control, including provision and delivery of appropriate first-line medicines.
14 Based on analysis of tender data for the period from 1 August 2013 to 31 July 2015.
15 Based on analysis of tender data for the period from 1 April 2012 to 31 March 2013 (i.e. 1 024 400 patient boxes, under product codes PC-1 and PC-2). Procurement through RITES with Indian government funds, including World Bank loans. Excludes GDF procurement for India with donor funds.

In summary, given the many procurement channels for TB medicines—and the potential for unique procurement and quality requirements by purchaser—**global demand is effectively fragmented, and the purchasing power of any single procurer is limited**.

6.2.3. Price, formulation and competition in the first-line TB medicines market

Price

TB medicines for a standard first-line regimen are relatively inexpensive, costing roughly US$ 22/day from GDF (9, 89), US$ 28–32 through South African government tenders[16] (2, 3), and US$ 11 through Indian government tenders.[17,18] (5) Average costs reported to WHO are up to US$ 40 for low- and lower-middle income countries, and US$ 50 for upper-middle-income countries. Prices can vary partly due to costs such as freight, inspection, agent fees, insurance and preference for domestic manufacturers. (1) According to WHO, low- and lower-middle-income countries reported an average cost of up to US$ 40, and upper-middle-income countries reported an average cost of US$ 50 in 2011.

FDCs

Public-sector programmes in all but one of the high-burden countries use FDC medicines to treat TB.[19] (86) Procurement data, where available, also show a tendency to use FDCs, in line with WHO recommendations. FDCs decrease the pill burden significantly, ensure adequate dosing and discourage inappropriate use of single-component monotherapy (i.e. loose pills). (30) In this way, use of FDCs may improve adherence to a full course of treatment with appropriately dosed medicines, leading to better health outcomes for individual patients and decreased likelihood of drug resistance. GDF promotes standardized patient treatment through use of FDCs and patient kits. GDF reports that two- and four-component FDC products accounted for almost 70 % (by value) of first-line TB medicines procured by GDF in 2012–2013. (82) Analysis of South African government procurement shows a similar preference for FDCs, with 72 % FDC versus 28 % loose pills (by value) for contracts awarded for the period from 1 August 2011 to 31 July 2013. (2, 3)

Competition

Manufacturer market share is concentrated, with different manufacturers meeting demand from various procurers. Four manufacturers—Lupin, Macleods, Strides and Reig Jofre—account for almost 90 % of 2012 first-line TB medicines purchases reported in the PQR (used as a proxy for donor-funded procurement). Two manufacturers—Sanofi-Aventis South Africa Pty and Sandoz Pty—account for 99 % of first-line TB medicines contracts awarded by the South African government for the period from 1 August 2013 to 31 July 2015. Notably, there is very limited overlap in manufacturers serving the donor-funded and South African government markets (refer to Figure 12).

For procurement of first-line TB medicines, the Indian government awarded contracts almost exclusively to Sandoz in 2010–2011 (97 % market share, by value, for procurement of first-line patient kits PC-1, PC-2 and PC-4, and loose isoniazid PC-7) and exclusively to Lupin in 2012–2013 (100 % market share, by value). The switch from Sandoz to Lupin may have been driven by price. Sandoz won the 2010–2011 contracts with bid prices of 6 % less than Lupin's. However, by 2012–2013, Sandoz bid prices had increased sharply, exceeding Lupin's by 7–9 %. Contracts in 2012–2013 were awarded to Lupin (refer to Figure 13).

---

16 Delivered price; equivalent to US$ 20–28 (excluding 14% VAT). Based on analysis of contracts awarded by the South African government for the period from 1 August 2011 to 31 July 2013, for a standard first-line regimen with two- and four-component FDC products.

17 Price excludes 5% VAT and sales tax. Based on analysis of Indian government purchases of first-line TB medicines from 1 April 2012 to 31 March 2013, for patient kits of multiblistered tablets. Procurement through RITES with Indian government funds, including World Bank loans. Excludes GDF procurement for India with donor funds. For detail of calculations, refer to Appendix 1.

18 Note that products can vary; these prices do not necessarily reflect a like-for-like comparison on products or QA requirements.

19 As of 2011, India did not procure FDCs in the public sector, and more recent data suggest this situation persists.

Figure 12. Relative market share of first-line TB medicines manufacturer, by value, Global Fund vs South African government procurement

First-line PQR from 1 January 2012
(includes all data verified in PQR by 23 May 2014

First-line South Africa tender
1 August 2013–31 July 2015
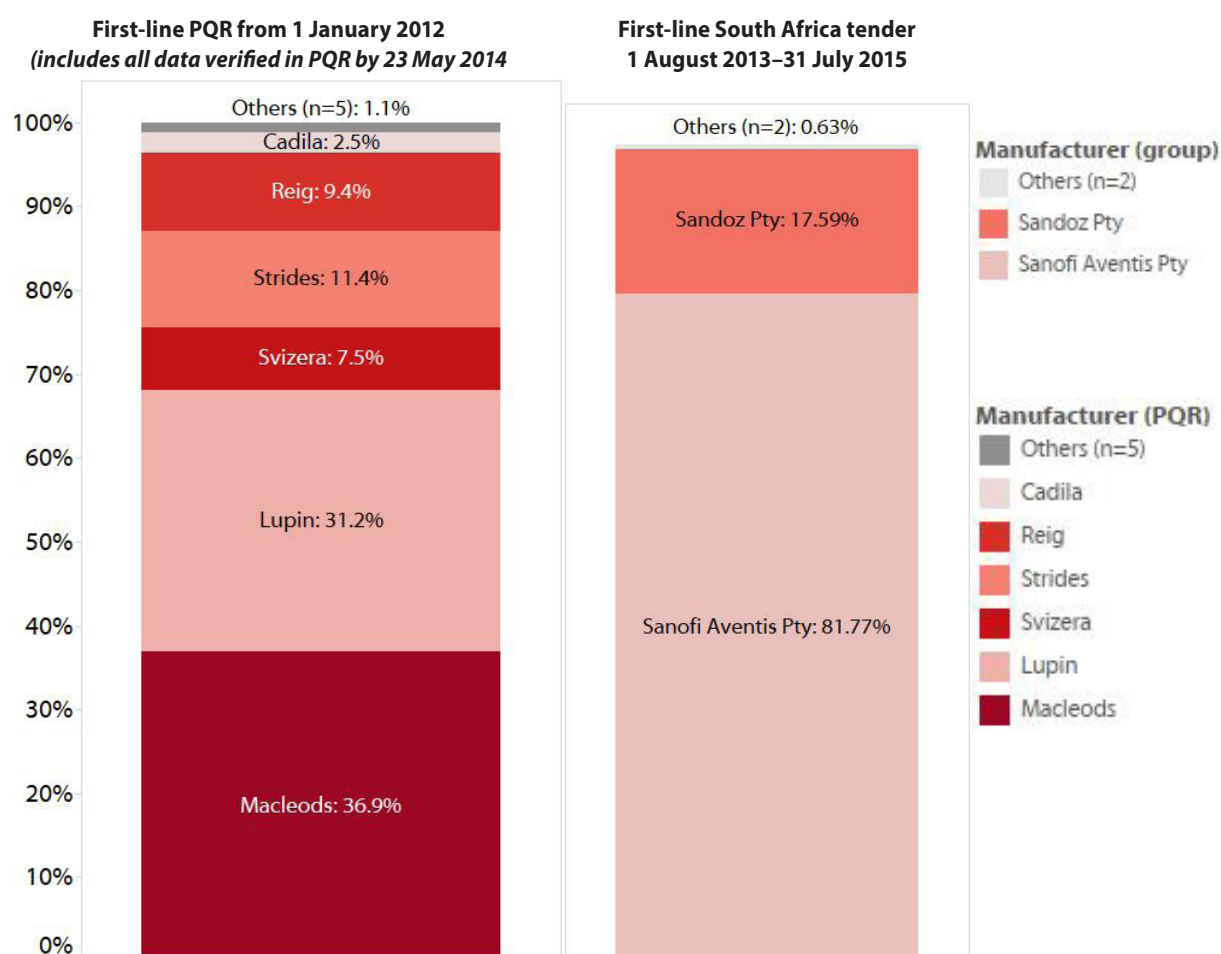
Sources and notes: Global Fund PQR: UNITAID analysis of the Global Fund PQR database, 2013 transactions, excluding those pending verification. South Africa: analysis of bid HP01-2013TB; (2) and bid HP01-2013TB/01. (3) Used exchange rate as of 8 June 2013 (date first contract signed): 9.9141 ZAR = US$ 1. (13)

Figure 13. Indian government procurement of first-line TB medicine kit, contract volume and prices

Indian government procurement of first-line TB medicine kit PC-1 (volume of treatment courses and cost per course)
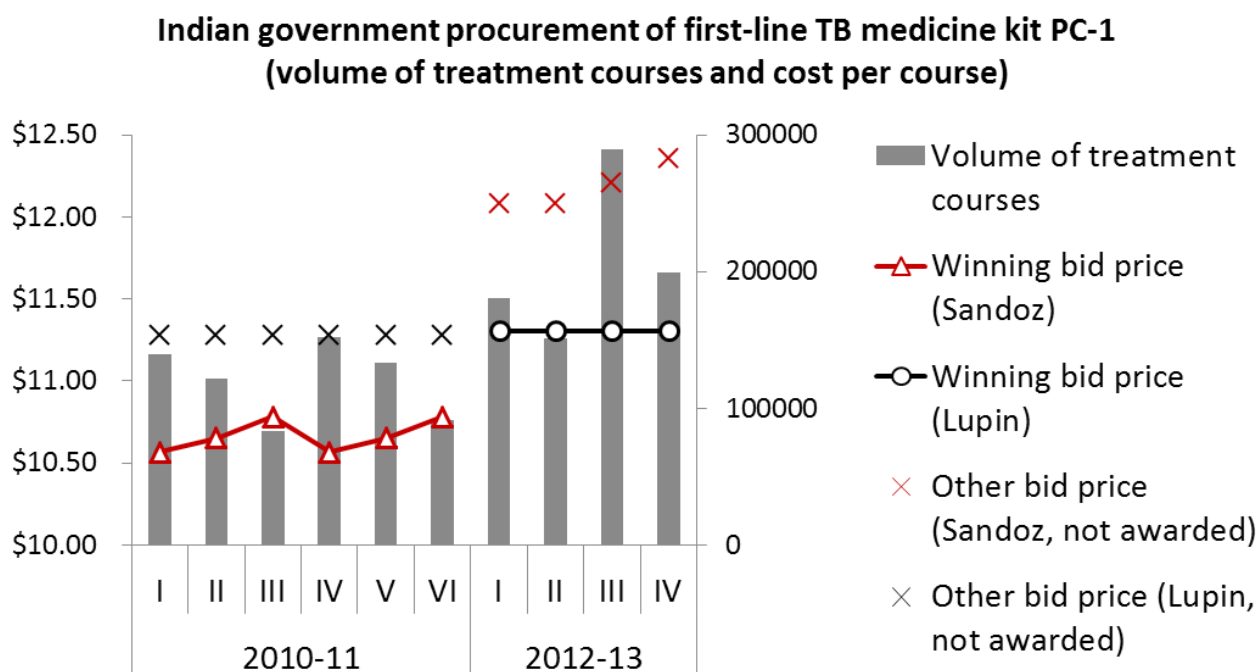
Sources and notes: Indian government volumes and prices derived from analysis of Indian government data obtained through request for information by Access Health International. Contracts awarded in 2011–2012 and 2012–2013 Indian financial year. Used exchange rate: 0.02161 INR = US$ 1 (x-rates.com). Unit prices shown exclude 5% VAT and sales tax. (5)

Quality assurance of first-line TB medicines can vary by product and manufacture (refer to Box 2). Appendix 2, Table A 1 summarizes first-line TB medicine formulations in the WHO Model List of Essential Medicines and/or WHO standard treatment guidelines, and the number of formulations that have been QA by WHO PQ, a stringent regulatory authority, or ERP hosted by WHO on behalf of the Global Fund.

In 2013, shortages threatened the supply of isoniazid in some countries (e.g. India; United States). (93) Since 2005, shortages have also been reported for rifampicin, rifabutin and streptomycin. (94) In general, however, the first-line TB medicines market is relatively stable and characterized by mostly generic, low-cost products. While there appears to be scope for consolidation of demand and harmonization among the many purchasers of first-line TB medicines, market shortcomings are more pronounced in other segments of the TB medicines market. Treatment of MDR TB in adults and treatment of TB in children represent much smaller segments of the TB medicines market by volume, relative to first-line treatment in adults. However, these market segments are complex and fragile, with numerous and severe market shortcomings. The emphasis of the rest of this document, therefore, is on MDR-TB medicines (section 6.3) and paediatric TB medicines (section 6.4).

6.3. Market for medicines to treat MDR TB

6.3.1. Introduction

The MDR-TB medicines market segment is small and fragmented. From a manufacturer perspective, market potential is low—though recent data (2012–2014) indicate a rapid increase from a small base (9), and increased attention from manufacturers as a result. Features of the QA MDR-TB medicines market include products that are much more expensive than those used for first-line treatment (US$ 1800–6,000 + versus US$ 22 per regimen) (51), longer treatment duration (20–24 versus 6 months) (30, 31), and extremely low (but growing) volumes. In 2012, only 77 321 patients were enrolled on second-line treatment (9), approximately 1 % of the number patients receiving first-line medicines. Even if all estimated cases of

DS TB and MDR TB were enrolled on treatment, the number of MDR-TB patients would account for about 5 % of the total.[20] This small market is further fragmented by many procurement channels and a wide range of complex treatment regimens, in which various products and formulations are combined.

The 2011 WHO guidance outlines principles of MDR-TB treatment. (31) In practice, however, standardization of treatment is minimal. Excessive variation in MDR-TB treatment regimens, and evidence needed to determine if and how streamlining is possible, was a key theme of the UNITAID 2013 Tuberculosis Market Forum (refer to Box 3).

6.3.2. Buyers of MDR-TB medicines

In 2012, national governments were significant purchasers of MDR-TB drugs, as shown in Figure 7. WHO data suggest that, overall, national treatment programmes account for about three quarters of all spending (by value) on MDR-TB drugs and management.[21] (1) In many countries, the shift from donor funding to greater country ownership is more established for first-line TB medicines than for MDR-TB medicines. However, much of the estimated MDR-TB burden globally occurs in middle-income countries, including BRICS, where national governments fund the majority of TB care and control[22] (1) and are actively scaling up care for MDR TB. Indeed, just three of these countries—China, India and the Russian Federation—accounted for over 55 % of the estimated 300 000 MDR-TB cases in 2012.[23] (9) Tender data show that, for the period from 1 August 2013 to 31 July 2015, the South African government alone procured US$ 48.5 million of MDR-TB medicines. (2, 3) Donors also play a critical role in the procurement of MDR-TB medicines: in 2013, GDF reported procurement of approximately US$ 128 million of grant-funded MDR-TB medicines.[24] (82) A 2013 publication estimated that GDF procurement, for both donor-funded and public non-donor segments, accounted for 31.7 % of all reported MDR-TB cases, or 4.2 % of estimated cases (by volume). (85) While accounting for only a small portion of the overall MDR-TB medicines market, GDF purchases are increasing (by 52 % from 2011 to 2012, with 29 800 treatment courses supplied in 2012). (85) As noted above, further analysis of GDF's evolving role in procuring TB medicines has been conducted, with publications forthcoming.

Provision of medicines in the private sector is thought to be less significant for MDR TB than for DS TB, with many MDR-TB drugs and even some drug classes not available. (23) As noted above, however, visibility on private-sector market dynamics is limited: market size, treatment patterns and other dynamics are often poorly understood. Given the complexity of MDR-TB care, the private sector may refer MDR-TB patients back to the public sector.[25] A study using 2006 data estimated the value of medicines purchased for MDR TB in five countries to be US$ 37 million, but these estimates are plagued by uncertainty about the percentages of these drugs being used for other indications. (95) Improved global estimates and more current data are unavailable.

As with first-line TB medicines, each purchaser of MDR-TB medicines can have unique requirements for quality assurance, effectively fragmenting global demand. Refer to Box 2 and Appendix 2, Table A 2 for further detail.

Similar market distortion—e.g. excessive or nontransparent fragmentation—can occur if each purchaser of MDR-TB medicines applies unique requirements for procurement, or if variation in medicines formulations is excessive. Refer to section 6.1 for further detail.

---

20 That is, 450 000 estimated cases of MDR TB and 8 600 000 estimated cases of DS TB in 2012.

21 Funding for "TB care and control" includes spending on both drugs and programmatic aspects of MDR TB.

22 Donors contribute 60% of all TB funding in the 17 high-burden countries outside BRICS, but only about one third of the total in BRICS.

23 Among patients with pulmonary TB known to NTPs.

24 This exceeds the value of the donor-funded segment estimated from PQR data (US$ 39 million Global Fund, US$ 44 million all donors), likely due to reporting differences. It should also be noted that the GDF 2010 annual report shows direct purchase of MDR-TB medicines far outpacing grant purchases (US$ 41.2 million versus US$ 15.9 million in 2010), as countries transitioned from grants to Global Fund or other sources of funding.

25 Many patients still pay out of pocket for MDR-TB medicines in the public sector as most NTPs do not provide free of charge.

6.3.3. Price, competition and supply in the MDR-TB medicines market

Price

MDR-TB medicines are expensive, and price variation can be significant across purchasers. Treatment with a QA regimen costs approximately US$ 1800–6000 + per patient per course of treatment from GDF. (4, 23) National treatment programmes often pay less: in 2011, based on country data reported to WHO, MDR-TB drugs cost national treatment programmes US$ 1200–3800 per patient. For 2013, national programmes in low-income countries budgeted US$ 2600 per patient; upper-middle-income countries, US$ 4700. (1) Limited conclusions can be drawn from these price points, however, as differences in quality requirements, funding sources, regimens and other factors may drive this variation. For example, differences in quality requirements hinder direct price comparisons (refer to Box 2). QA kanamycin from GDF is US$ 0.90/vial (powder for injection, 1 g vial), (GDF online catalogue), while the Indian government procured a non-QA product from Vital Healthcare at US$ 0.26/vial (excluding 5% VAT and sales tax) in 2011–2012. (Access Health India Market Analysis, 2013).[26]

Competition

As is the case for first-line TB medicines, it is notable that there appears to be very limited overlap in manufacturers serving the donor-funded and South African government markets; refer to Figure 14 (note: some overlap may exist where manufacturers supply to South Africa via a local subsidiary or distributor). Given the complexity and diversity of MDR-TB regimens, and the highly fragmented nature of MDR-TB medicines procurement, analysis of market consolidation or manufacturer market share for multiple drugs is of limited utility. Product-specific issues are, therefore, the focus of the rest of this section.

---

26 For example, differences in quality requirements hinder direct price comparisons (refer to Box 2). QA kanamycin from GDF is US$ 0.90/vial (powder for injection, 1 g vial), (GDF online catalogue), while the Indian government procured a non-QA product from Vital Healthcare at US$ 0.26/vial (excluding 5% VAT and sales tax) in 2011–2012. (Access Health India Market Analysis, 2013).

Figure 14. Relative market share of MDR-TB medicines manufacturer, by value, Global Fund vs South African government procurement
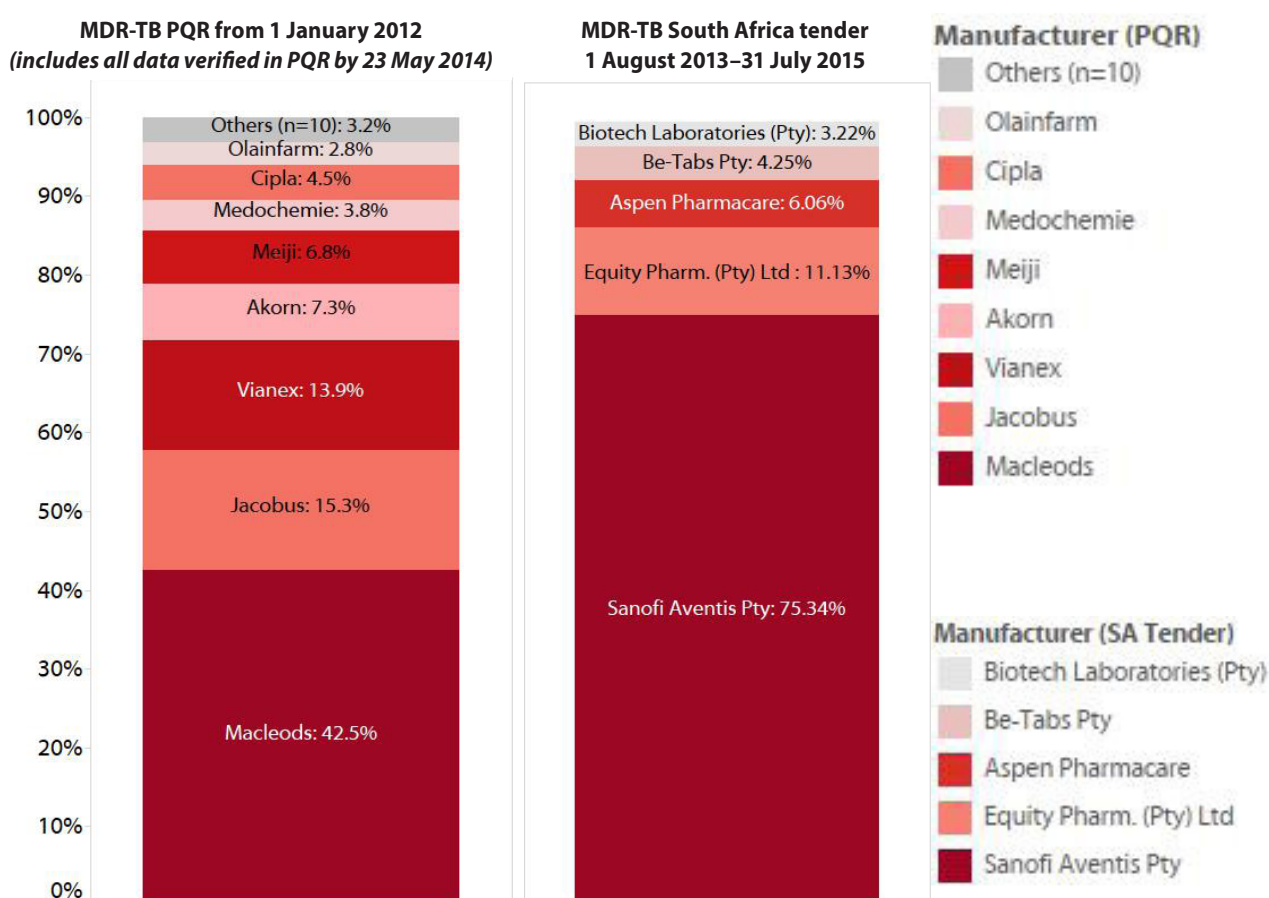
Sources and notes: Some overlap possible where manufacturers supply to South Africa via a local subsidiary or distributor. Global Fund PQR: UNITAID analysis of the Global Fund PQR database, 1 January 2012–23 May 2013, excluding those transactions pending verification. South Africa: analysis of bid HP01-2013TB and bid HP01-2013TB/01. (2, 3) Used exchange rate as of 8 June 2013 (date first contract signed): 9.9141 ZAR = US$ 1. (13)

Appendix 2, Table A 2 summarizes MDR-TB medicine formulations in the WHO Model List of Essential Medicines and/or WHO standard treatment guidelines, and the number of formulations that have been QA by WHO PQ, a stringent regulatory authority, or ERP hosted by WHO on behalf of the Global Fund. For MDR-TB medicines with few QA options eligible for procurement with donor funds, concentrated supplier power and limited competition can exacerbate the price differential between medicines with quality assurance and those of an uncertain quality standard.

Over 80% of the overall value of MDR-TB medicines procured with Global Fund funding in 2012 was driven by the following key products: capreomycin; PAS; moxifloxacin;[27] kanamycin; and cycloserine. To date, there has been only very limited procurement of bedaquiline and delamanid, but these new drugs have the potential to account for a large percentage of the value of the future market depending on price and positioning relative to other MDR-TB treatments. Trends in specific product markets, highlighted in this section, include:

- capreomycin: price, quality and supply instability; improving trends, but API supply still limited;
- PAS: demand fragmentation across multiple formats; API supply limitations;
- moxifloxacin: continued price reductions with emergence of generic alternatives;
- kanamycin: price, quality and supply instability; API supply limitations.

Cycloserine, while a cost driver of MDR-TB treatment, has a relatively secure QA supply of finished pharmaceutical product. Other products that currently do not constitute a significant share of MDR-TB medicines procurement (by value) remain important treatment options—and improved market dynamics may become increasingly important. For example, with clofazimine a component of study regimens (e.g. in the STREAM trial; also being considered for inclusion in endTB), demand may be expected to increase significantly if positive results support more widespread use. Although price is not considered an access barrier, producer Novartis supplies clofazimine for off-label use in TB only on a named-patient basis. Generic competition is possible, but current manufacturers do not offer QA product. (23) In addition, levofloxacin could play a more dominant role as a fluoroquinolone in the recommended MDR-TB treatment regimen since its cost has continued to decrease over the past two years. In July 2014, the API for levofloxacin was approved for WHO PQ, which will likely contribute to improved quality and stability of supply and could result in further reductions in overall cost of the finished product formulations. (96)

Supply issues affecting several MDR-TB medicines include availability of API. Lack of API sources and small volumes jeopardize the viability of API production for MDR-TB medicines. Limited competition in the API supply market has downstream effects on finished product prices and supply stability. Refer to Box 5 for further detail.

---

27 Price expected to decrease with increasing competition among generic versions; refer to Figure 14 and Figure 15.

Box 5. MDR-TB medicines market dynamics related to production of APIs

APIs play a key role in the quality and cost of MDR-TB medicines. However, API markets for MDR-TB medicines remain opaque because data on manufacturers and costs are not gathered systematically. API production for MDR-TB medicines (particularly injectables) can be complex, technically challenging, environmentally unfriendly, and scale and capital intensive (e.g. capreomycin API requires a sterile fermentation process). The majority of APIs for TB (and MDR-TB) medicines are produced in China, due to its advanced fermentation technology and manufacturing cost position.

Supply sources

There are few QA API suppliers for most MDR-TB products; for some, a monopolistic API supply market exists. On the other hand, global procurement volumes are small and **even a single API manufacturer often cannot run at efficient scale**. While the dynamics of each product are very different, lack of API supply sources and small volumes together have put supply sustainability for MDR-TB medicines in question and, in some instances, have led to very high prices for MDR-TB medicines. New regulatory standards for injectable drugs in China have introduced additional challenges for manufacturers of some products (e.g. capreomycin).

Empirical models to understand drivers of competition in API markets suggest that **MDR-TB products used to treat infectious diseases other than MDR TB have vibrant and competitive API supply markets**. For other MDR-TB medicines—i.e. those used primarily to treat TB—structural determinants (e.g. low volumes; higher transaction costs) lead to a lower number of API manufacturers. Data from interviews[1] revealed that low overall demand, high volatility of demand, complex production processes and more rewarding opportunities in other API markets can make **MDR-TB API a rather unattractive market for new entrants in some product markets**, with specific issues detailed in the following sections.

Prices

Many factors can drive high prices, including production at less than minimum efficiency scale, lack of competition in an API or finished product market and high transaction costs. Empirical models[2] confirm that the **degree of API competition is strongly correlated with finished product price**. Keeping other factors constant, MDR-TB medicines with fewer QA API suppliers tend to have higher prices.[3] Payment terms are another important determinant of finished product price: **prices can be significantly lower for orders with full or partial advance payment**. This suggests that higher transaction costs of operating in the market are an important, but often neglected factor in attempts to reduce prices for MDR-TB medicines.

1 Quasi-structured interviews with current or potential API manufacturers for MDR-TB medicines.
2 Models used finished product prices from the Global Fund PQR database (using data until 2010).
3 Variation by product and supplier base can be large, however. For example, API costs appear to be a less significant driver of finished product costs for some products, particularly injectables, when compared to other products manufactured through basic chemical synthesis.

Source: Analysis for UNITAID: Yadav (2012). (97)

Capreomycin

Issues with technology transfer and supplier transitions have in the past compromised market function for capreomycin. **More recent trends suggest market stabilization, but API supply is still limited**. Capreomycin prices for donor-funded procurement nearly doubled between 2010 and 2011, as developer Eli Lilly exited the market, selling its license to Akorn and ending subsidized pricing of the injectable drug. (89) In 2003, Eli Lilly committed to transfer its technology to companies in high-TB burden countries based on expectations of significantly increasing demand. Four generic manufacturers (Aspen, Hisun, Akorn and Vianex) were recipients of Eli Lilly's technology transfer. (98) Upon Eli Lilly's exit in mid-2011, however, Akorn became the only approved capreomycin manufacturer.[28] (99)

In 2011, procurers faced insufficient quantities of capreomycin due to Eli Lilly's exit and Akorn's challenges with scale-up. In addition, there is only one QA API supplier: Hisun in China. While alternative API manufacturers do exist, only Hisun has been approved by a stringent regulatory authority or WHO PQ. A complex, sterile fermentation process is required to produce capreomycin API, a potential barrier to entry for new manufacturers.

Following capreomycin approval in Spain in early 2012, Vianex became a second approved finished product manufacturer, and prices dropped over 30% following GDF price negotiations. (23, 100) Thus, to date, two finished product manufacturers and one API manufacturer have received stringent regulatory author-

28 Three manufacturers are undergoing WHO PQ, but were not approved as of August 2014.

ity approval. Five other manufacturers have submitted dossiers for WHO PQ, suggesting a broader base of finished product manufacturers in the future. (23, 101)

In addition, however, API manufacturer Hisun received WHO API PQ in April 2014. With the potential for vertical integration of this sole QA API manufacturer, recent trends in market stabilization could potentially be threatened if other API suppliers are not established or used. While vertical integration could potentially destabilize this currently functional market, more work is needed to understand the likely net impact on market dynamics.[29] For example, if a QA API manufacturer develops capacity to produce finished product, then that integrated manufacturer may realize manufacturing efficiencies leading to potential to reduce costs—but also has significant ability to control the market (and could, for example, discontinue API supply to other competitor finished product manufacturers and limit competition). Figure 15 and Figure 16 illustrate directional price and volume trends over time, based on analysis of the PQR database. In particular, Figure 15 illustrates the dramatic effects of monopoly supply on capreomycin price—and the subsequent moderation with entry of additional supplier Vianex.

The South African government sources capreomycin from a single local manufacturer, Aspen (2, 3), at a delivered price of over US$ 12 per 1 g vial. Adjusted to exclude 14 % VAT, this is still over 50 % higher than the 2012 weighted average cost to GDF of the Akorn product, and more than double that of the Eli Lilly subsidized product. (In considering bids for national tenders, South Africa requires local registration and considers price and other factors, including promotion of local manufacturing.) (102)

Figure 15. Capreomycin 1 g vial cost and volume, Global Fund procurement 2009–2012 (median cost and volume procured) (US$)
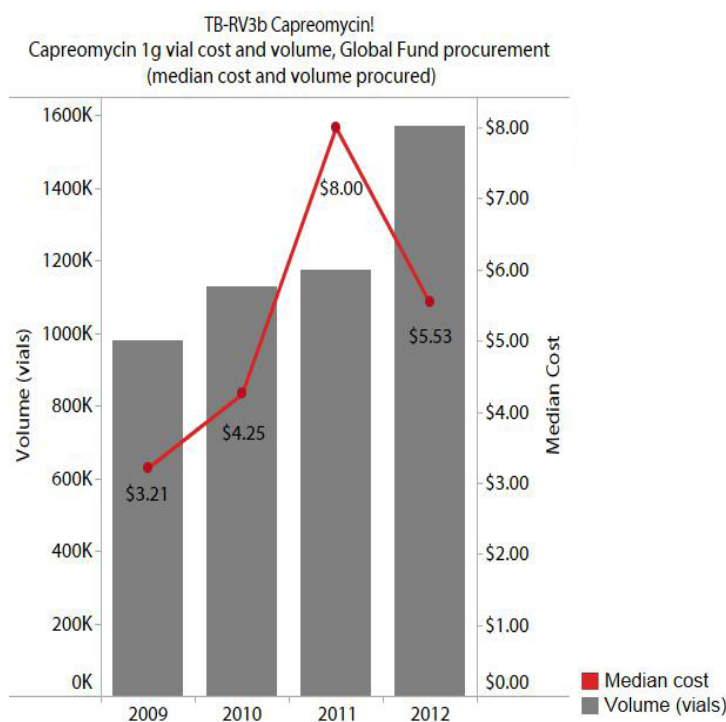
Note: Refer to Appendix 1 for further detail on methodology including median cost calculations.
Source: UNITAID analysis of the Global Fund PQR database, 2009–2012 transactions, excluding those pending verification.

---

29 There have been examples (i.e. the cycloserine market, etc.) where vertical integration did not result in market destabilization and the price of the finished product actually decreased.

Figure 16. Capreomycin 1 g vial cost and volume, Global Fund procurement 2009–2012 (median cost and volume procured, by manufacturer) (US$)

Notes: Eli Lilly supplied GDF at a subsidized price of US$ 4.00 until exiting the market and exhausting its stock. GDF now sources from Akorn or Vianex, the latter a second QA manufacturer as of 2011. (23) GDF lists 2014 catalogue prices of US$ 4.95–6.25, indicating further recent decreases. Refer to Appendix 1 for further detail on methodology including median cost calculations.
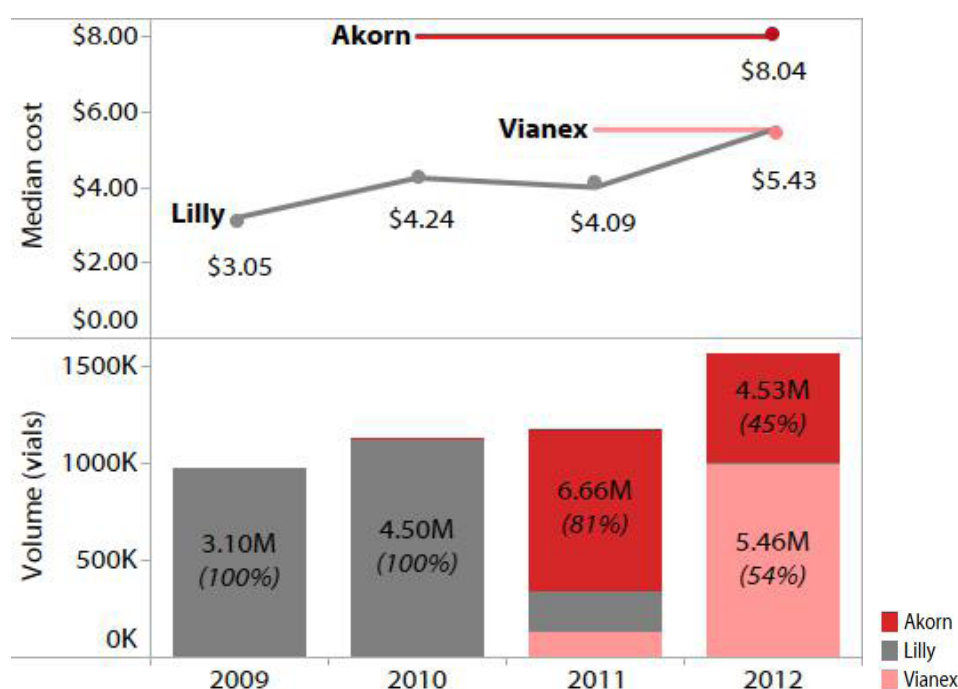
Source: UNITAID analysis of the Global Fund PQR database, 2009–2012 transactions, excluding those pending verification.

PAS and PAS sodium

The supply of PAS products is vulnerable: despite QA product from multiple suppliers, the demand is fragmented across formats that are not easily interchangeable[30] and API supply is limited, with the potential for further concentration. Only one QA manufacturer (Jacobus) supplies PAS, and only two—Macleods and Olainfarm—supply PAS sodium. (23) PAS 4 g sachets make up the bulk of procurement funded by the Global Fund. PAS sodium (60% weight/weight) is available in 9.2 g sachets and 100 g containers of granules, and in 5.52 g sachets of powder for solution.[31] Following WHO PQ of Macleods PAS sodium product in 2009, demand increased. However, demand subsequently dropped again in 2011, in part due to WHO guidelines recommending use of PAS (versus other oral bacteriostatic drugs) "only if an additional drug is needed to achieve a five-drug regimen or if ethionamide or cycloserine cannot be used or are unlikely to be effective". (31)

Médecins sans Frontières reports prices ranging from US$ 1.3–1.5 across PAS products: PAS 4 g sachet (Jacobus); 9.2 g sachets of PAS sodium 60% weight/weight granules (Macleods); and 5.52 g sachets of PAS sodium powder for solution (Olainfarm). (4, 23, 103) Recent trends in directional price and volume, based on analysis of the PQR database, show modest decreases (refer to Figure 17). However, the price of PAS is not likely to decrease significantly in the near future as no other sources are currently in the pipeline.[32] (23) However, due to new stability data from Jacobus, GDF now offers PAS without cold chain storage requirements, increasing its utility as a stockpiled drug and more broadly in countries where limited resources caused storage complications.[33]

---

30 Review of the PQR database, 2009–2012 transactions, showed that most countries procure only PAS; very few appear to procure both PAS and PAS sodium (e.g. Pakistan in 2010, Kazakhstan in 2011 and 2012).

31 5.52 g PAS sodium is equivalent to 4 g PAS.

32 It should also be noted that products do not fully compete in a market that is fragmented across multiple formats that are not easily interchangeable, further decreasing demand.

33 Previously, PAS (PASER) had to be kept at under 15 oC, requiring cold chain storage; new data has demonstrated the product's stability at room temperature adjusting the storage requirement to under 25 oC no longer requiring cold chain.

Figure 17. PAS (4 g) and PAS sodium equivalent (5.52 g) cost and volume, Global Fund procurement 2009–2012 (median cost and volume procured, by manufacturer) (US$)
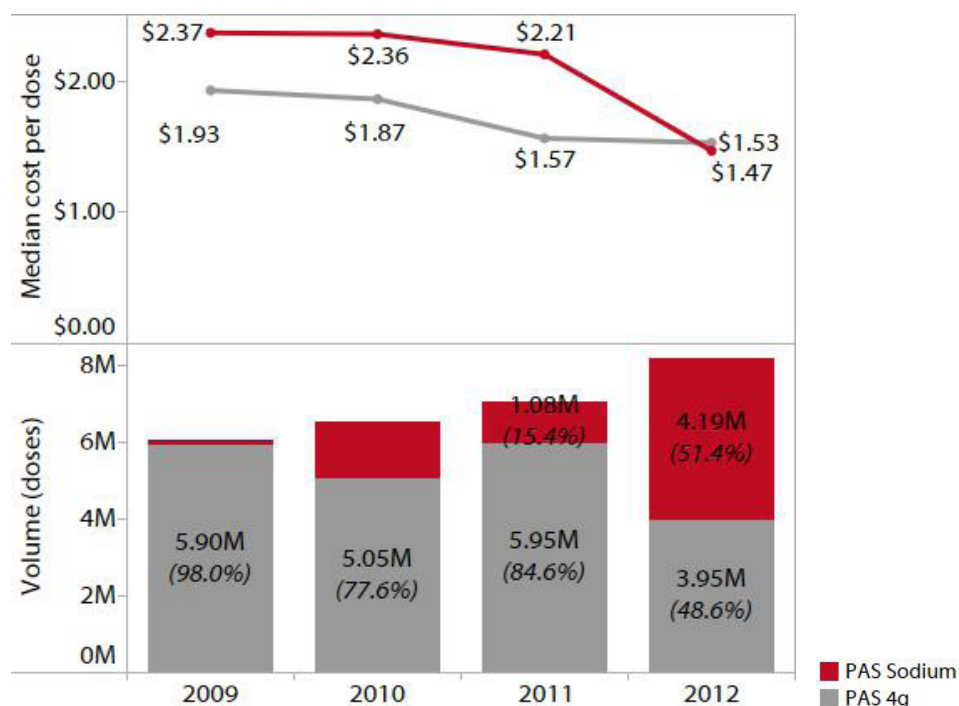
Notes: 5.52g PAS sodium is equivalent to 4 g PAS. Where PQR reports procurement of PAS sodium in 100 g containers, figures were adjusted to reflect amount equivalent to PAS 4 g (i.e. a single dose).

Source: UNITAID analysis of the Global Fund PQR database, 2009–2013 transactions, excluding those pending verification. Partial data only for 2013; included to show continuation of directional trends.

Moxifloxacin

Following the expiry of Bayer's basic patent in most countries, **the price of moxifloxacin has steadily decreased with the increased availability of QA generics**; refer to Figure 18 for directional volume and price trends, based on analysis of the PQR database. After receiving WHO PQ for its generic moxifloxacin product in November 2010, Cipla quickly gained market share at the expense of Bayer. Cipla's increase in market share appears to have moderated following decreases in the Bayer product price. Refer to Figure 19 and Figure 20 for directional trends evident from analysis of available transactions in the PQR data. Additional sources of QA generic moxifloxacin are becoming available, reinforcing downward price trends and supply security:

- The Global Fund ERP approved Macleods' generic product in 2012, and in 2013 it received WHO PQ. (ERP had also temporarily approved generic products from Hetero and Sandoz, with approval valid until November 2013 and May 2014, respectively). Four additional manufacturers are currently under review for WHO PQ. (23)

- In India, a key patent blocking generic production was rejected, opening the market for increased generic competition. Generic moxifloxacin is already marketed in the Russian Federation. (23)

In its most recent tender, the South African government included estimates for 9.2 million moxifloxacin tablets for the period from 1 August 2013 to 31 July 2015. (2, 3) However, price data are not provided in the tender document.

Overall, considering the size of the pipeline and the significant external market (given that moxifloxacin is co-indicated for use with other infections), moxifloxacin is likely to achieve effective and efficient market dynamics in the relatively near term.

Figure 18. Moxifloxacin 400 mg tablet cost and volume, Global Fund procurement 2009–2013 (median cost and volume procured) (US$)

Notes: Partial data only for 2013; included to show continuation of directional trends. Refer to Appendix 1 for further detail on methodology including median cost calculations.

Source: UNITAID analysis of the Global Fund PQR database, 2009–2013 transactions, excluding those pending verification.

Figure 19. Moxifloxacin 400 mg tablet manufacturer market share, by volume
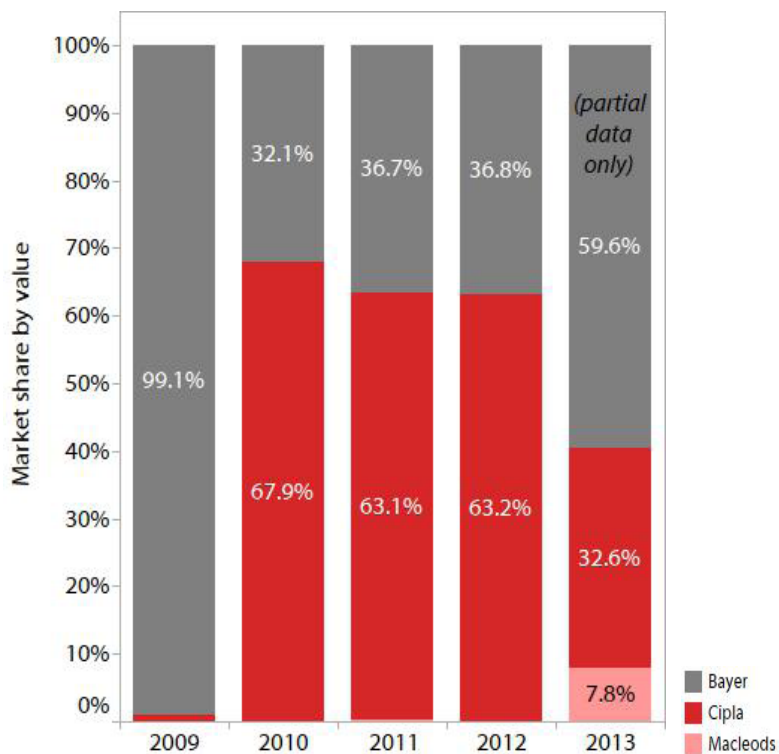
Note: Partial data only for 2013; included to show continuation of directional trends.
Source: UNITAID analysis of the Global Fund PQR database, 2009–2013 transactions, excluding those pending verification.

**Figure 20. Moxifloxacin 400 mg tablet cost and volume, Global Fund procurement 2009–2013
(median cost and volume procured, by manufacturer) (US$)**
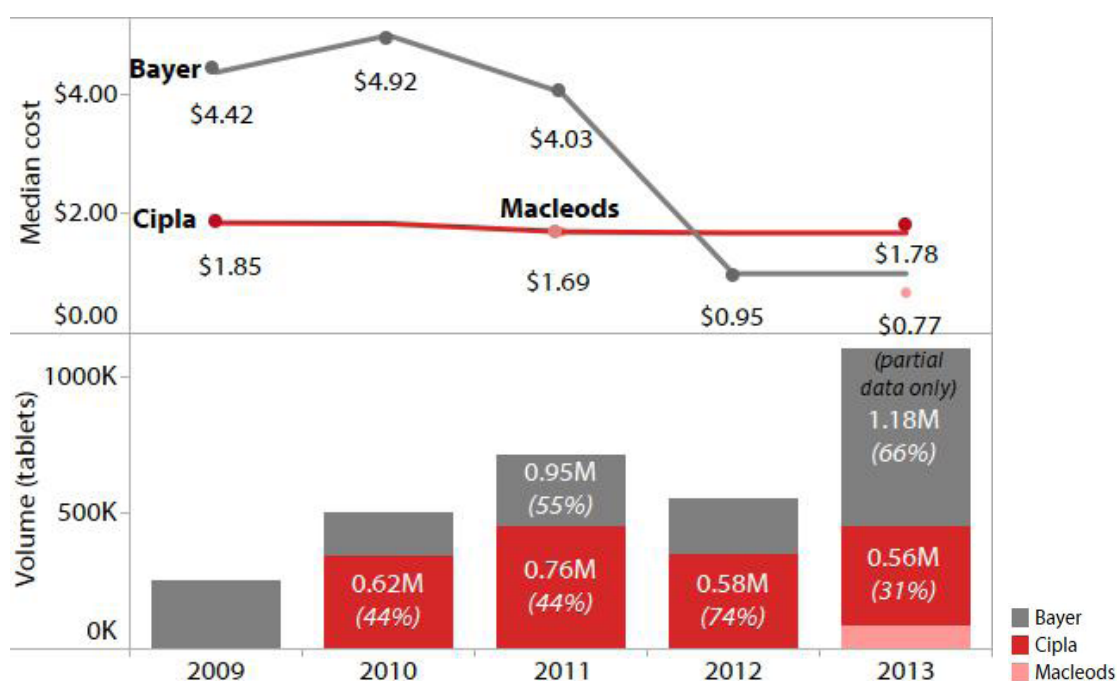
Notes: Partial data only for 2013; included to show continuation of directional trends. The median cost was calculated by number of transactions; when calculated by number of units, the Bayer median cost was US$ 4.70 in 2009 and US$ 1.00 in 2013. Refer to Appendix 1 for further detail on methodology.

Source: UNITAID analysis of the Global Fund PQR database, 2009–2013 transactions, excluding those pending verification.

Kanamycin

Kanamycin, like capreomycin, has been subject to price and supply instability linked to API production. Although no current kanamycin sources are WHO PQ (two formulations are currently under review), GDF sources QA kanamycin, approved by stringent regulatory authorities, from Panpharma (France) and—since 2010—Meiji (Japan). QA kanamycin supply was disrupted in 2009 due to an API manufacturing issue. GDF identified Meiji as an alternative supplier of QA kanamycin in 2010, but at a higher price. Figure 21 illustrates the supply volatility caused by these disruptions (from 2009). A steady supply of QA kanamycin API is needed to stabilize the finished product market, but few manufacturers have been capable of producing the API, which requires specialized fermentation processes and sterile conditions. Supply instability in the finished product, therefore, persists, although new sources of kanamycin API are expected and may alleviate some supply constraints and concerns. (23)

**Figure 21. Kanamycin 1 g vial cost and volume, Global Fund procurement 2009–2012,
(median cost and volume procured, by manufacturer) (US$)**

Notes: Analysis considers price trends of all 1 g formulations reported through PQR (includes 1 g, 1 g/4 ml, 1 g/5 ml). Removed Meji 2009 price (based on only one transaction). Refer to Appendix 1 for further detail on methodology including median cost calculations.
Source: UNITAID analysis of the Global Fund PQR database, 2009–2012 transactions, excluding those pending verification.
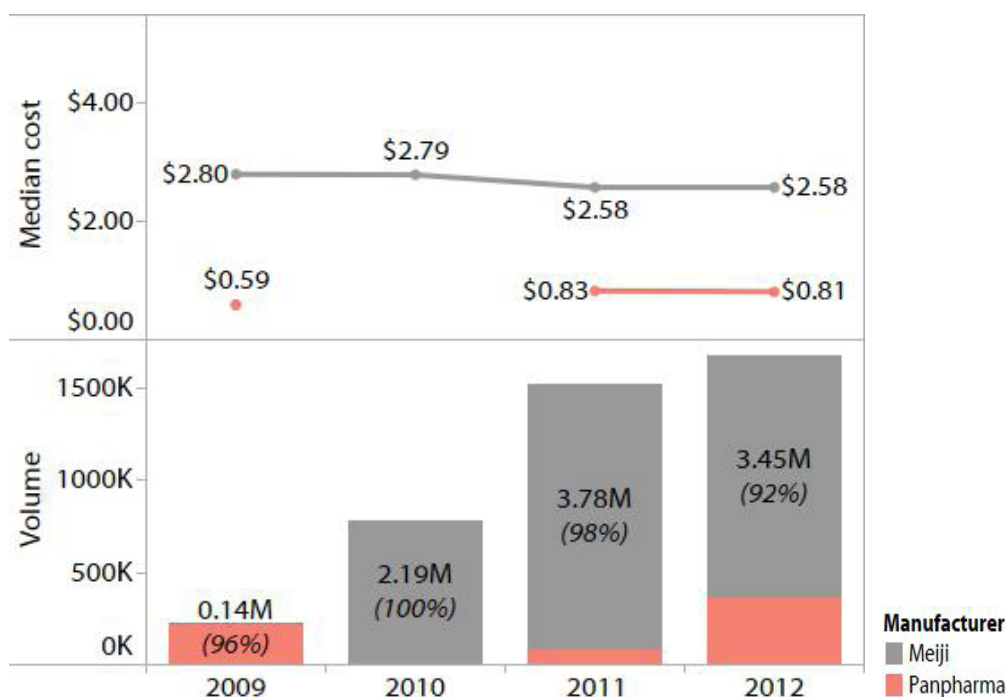
As with capreomycin, the South African government sources kanamycin from a single local manufacturer, but does not have the same quality requirements as donors (refer to Box 2). Biotech Laboratories (Pty) Ltd, a local South African manufacturer supplying 10 countries in southern Africa, supplies kanamycin at a delivered price of US$ 0.87 per 1 g injection, 3 ml vial, or US$ 0.76 excluding 14 % VAT—3.4 times lower than the 2012 weighted average cost to GDF from Meiji (as reported in the PQR data), and 5 % lower than the Panpharma product.

Cycloserine
When Eli Lilly stopped supplying subsidized cycloserine in 2006, the market was left with a single approved manufacturer who continued to sell at its higher price. However, supply is currently relatively secure: prior to exiting the market, Eli Lilly completed technology transfer to three generic companies (Aspen, Chao Center and Biocom) to produce cycloserine finished product, and to Shasun to produce cycloserine API. Currently, Aspen, Biocom, Dong A, Shasun and Macleods are WHO PQ suppliers of cycloserine. Médecins sans Frontières notes that additional manufacturers are currently under review for WHO PQ. (23) New prequalified API sources are expected to make the API market more competitive, especially given the limited growth of the cycloserine API market thus far. Preliminary estimates suggest that API makes up 38 % of the finished product cost, indicating additional potential to optimize scale and improve efficiency of production. (97) Refer to Box 5 for further discussion of market issues related to MDR-TB APIs.

6.4. Market for paediatric TB medicines

6.4.1. Introduction

The market for paediatric TB medicines is small, fragmented and fragile. Volumes are extremely low: although TB is one of the top 10 causes of death in children, with an estimated 1 million children needing treatment each year, very few cases of paediatric TB are detected and treated. In 2012, only 349 000 cases of paediatric TB were reported to NTPs. (9)

WHO released figures on the burden of paediatric TB for the first time in 2012, estimating that there were 490 000 cases of TB in children under 15 in 2011; there were an estimated 530 000 cases in 2012. However, these estimates assume that the case detection rate in adults (66 % of all cases is detected) also applies to children—i.e. that the 349 000 cases of paediatric TB reported to NTPs suggests a total of 530 000 estimated cases. (9) A recent study used setting-specific models to estimate the global incidence of childhood TB and found that the number of new cases in 2010 was close to 1 million; almost three times the number of cases notified to NTPs and twice the number of cases estimated by WHO in 2012. This substantial discrepancy between reported and actual cases is largely due to challenges in diagnosing TB in children. (24)

Detection of TB in children is poor for a range of reasons. Sputum, which is the most common sample used to diagnose TB, is difficult for children to produce. Even when sputum is obtained, it often has a very low bacterial load—especially in children who also have HIV. Up to 95 % of children with TB do not return positive results for TB when tested with smear microscopy, the most basic and widely used TB diagnostic tool. (78, 104) Children are also more likely to develop complicated forms of the disease, where TB spreads beyond the lungs (such as TB meningitis). Box 6 outlines the impact of inappropriate diagnostics on the paediatric TB medicines market, as well as recent developments that could improve both detection and estimates of demand for TB medicines.

In an effort to improve treatment of paediatric TB, UNITAID is funding the TB Alliance, working with WHO and other partners, to lead development of appropriate formulations of TB medicines for children. Part of the grant focuses on market intelligence and knowledge-sharing to address data gaps and uncertainties—specifically, defining the market size, clarifying development and regulatory pathways, and engaging manufacturers to address the needs of this small but high-need market segment. (105) While an understanding of the market for paediatric TB medicines is incomplete given the reasons above, this section is an effort to document trends evident in available data and recent literature, for further consideration of needs and next steps.

Box 6. The impact of diagnostics on the market for paediatric TB medicines

The lack of appropriate diagnostics for children with TB leads to underdiagnosis or misdiagnosis, which in turn amplifies uncertainty on disease burden and demand for medicines. The burden of paediatric TB was estimated by WHO for the first time in 2012 (1), accounting for 6% of TB cases. However, newer estimates put the number of new cases of paediatric TB at almost 1 million cases per year—double the first WHO estimate. (24)

Given the challenges of definitively diagnosing TB in children, individualized approaches are often used, impeding comparison of methods and systematic reviews. Leading TB clinicians and researchers recently agreed on reference standards, clinical case definitions and methodological approaches for evaluating new diagnostic tools. The published consensus (106, 107), if broadly used, should support analysis of research and new diagnostic technologies and improve systematic, evidence-based reviews. Two additional guidance documents on paediatric TB were recently published. The Roadmap for Childhood Tuberculosis: Towards Zero Deaths outlines actions and investment needed to end childhood TB deaths. (79) The second publication updates WHO guidance on management of paediatric TB. (35)

Evaluations of existing technology in children and with alternative specimen types (108-111) have begun, but more studies are needed. Initial reports on the Xpert MTB/RIF assay showed lowered sensitivity in children versus adults, as expected. More recent studies (78, 112, 113) focused entirely on children show that the Xpert MTB/RIF assay had a significantly higher detection rate than smear microscopy, but was slightly less sensitive than culture.

WHO convened an Expert Group in May 2013 to review the current body of evidence for Xpert MTB/RIF. The resulting WHO policy update widens the recommended use of Xpert MTB/RIF, including for the diagnosis of paediatric TB and extrapulmonary TB from selected specimen types (cerebrospinal fluid, lymph nodes and other tissues), and recommends Xpert MTB/RIF as the initial diagnostic test in all individuals presumed to have pulmonary TB. (22)

A new pilot project in India will test at least 5000 children for TB, including MDR TB, in four cities over a three-month period. (114) Two ongoing studies focus on culturing alternate specimen types. An Oxford University study in Viet Nam is comparing blood and urine culture to traditional respiratory specimens for disseminated TB in children, with expected completion in 2014. In addition, a French National Institute for Health collaborative multisite study in Asia and Africa is evaluating improving TB diagnosis in HIV-infected children using interferon gamma release assay and different specimen types for culture. Meanwhile, advocates and experts alike are calling for increased research and development of new TB diagnostics appropriate for children. For further detail on technology and market issues related to TB diagnostics, refer to the UNITAID Tuberculosis Diagnostics Landscape.

Source: Carole Jefferson, analysis for UNITAID.

6.4.2. Buyers of paediatric TB medicines

If 1 million children need TB treatment annually, and assuming an average first-line regimen costs roughly US$ 30, the potential market for paediatric TB medicines could be up to US$ 30 million. With these assumptions, but only 349 000 cases of paediatric TB reported to NTPs **in 2012, the actual value of all paediatric TB medicines was probably approximately US$ 10 million**. (9)

Approaches to managing TB in children vary across purchasers, which include GDF, on behalf of donors and countries, and national governments. As with adult TB medicines, each purchaser of paediatric TB medicines can require a unique quality standard. Refer to Box 2 for detail. In contrast to adult medicines, however, there is a discrepancy between products that are recommended by WHO and those that are WHO PQ or approved by stringent regulatory authorities. That is, several QA FDCs of TB medicines are WHO PQ or available under the GDF Quality Assurance Policy, but none is aligned with the dosing recommended for children. The current WHO List of Essential Medicines for Children lists only single-component TB medicines, many of which are also used for adult treatment; (99, 115) tablets are often split or crushed to adjust the dose for children. In 2009, WHO issued guidance on how to achieve newly recommended paediatric dosing with available products, in April 2014 these guidelines were revised. (116) Refer to Table 8.

Table 8. QA TB medicines included in WHO guidance on dosing for children using currently available products

Product	Manufacturer	Quality assurance
rifampicin 60 mg + isoniazid 30 mg (2FDC) dispersible	Lupin, Macleods	WHO PQ
rifampicin 60 mg + isoniazid 30 mg + pyrazinamide 150 mg (3FDC) dispersible	Lupin, Macleods	WHO PQ
ethambutol 100 mg (single component) tablet	Macleods	WHO PQ

Notes: These guidelines have replaced the interim recommendations on dosing instructions for the use of currently available FDCs for children published by WHO in 2009; additional prequalified formulations are available—e.g. rifampicin 60 mg + isoniazid 60 mg (2FDC) tablet from Macleods, but are no longer included in WHO guidance on dosing for children.
Sources: WHO Guidance for NTPs on the management of tuberculosis in children; (35) list of WHO PQ. (117)

However, many diverse approaches to paediatric TB treatment persist. A 2013 study found that in 20 high-burden countries, only half had adopted 2010 dosing recommendations three years later—with efforts impeded by the lack of appropriate medicines. (118) With the advent of the revised recommendations in 2014, few countries will have facilitated adoption. As a result, various combinations of adult FDCs and loose pills are still used to achieve recommended paediatric doses. (25)

Given the significant overlap between TB medicines used for children and adults, it is often impossible to distinguish paediatric-specific procurement of TB medicines. Limited data exist regarding procurement of TB medicines specifically for children by GDF and South Africa. GDF reported procurement of 187 996 paediatric treatment courses in 2011[34] (92) and 162 000 in 2012 (81)—nearly half of the 349 000 cases of paediatric TB reported to NTPs in 2012, but less than 20% of the total estimate, if close to 1 million children need treatment each year. In its most recent tender for TB medicines, the South African government procured 49 million tablets, worth at least US$ 2.4 million, of paediatric TB medicines.[35] (2, 3)

6.4.3. Price and competition in the paediatric TB medicines market

Price
As noted above, the use of adult TB medicines for treatment of children hinders comprehensive price analysis. Other factors can further complicate direct price comparisons (e.g. differences in reported price levels; inclusion of shipping/insurance/tax; quality requirements). Limited available data, however, show significant apparent differences in cost of select paediatric medicines by procurement channel. QA rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible from GDF is US$ 0.036/dispersible tablet (4), while the South African government procured at US$ 0.09/dispersible tablet (excluding 14% VAT).

Competition
In the absence of appropriate paediatric TB medicines, ad hoc approaches to treating children with TB limit data availability and potential analysis of this market segment. However, as with first-line and MDR-TB medicines, different manufacturers appear to serve the donor-funded and South African government markets. Based on tender data for the period from 1 August 2013 to 31 July 2015, Sandoz Pty, Ltd is the exclusive supplier for South African government procurement of the only paediatric formulations listed above. GDF, on the other hand, procures WHO PQ rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible from Macleods.

---

34 In addition to 187 996 curative paediatric first-line treatment courses, GDF also reported procurement of 92 530 prophylactic treatment courses for children in 2011.
35 The volume of the procurement of rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible is a partial component of 146 867 intensive courses. For the 2FDC dispersible, intent for use in children was evident from dose, formulation and description of selected product (Rimactazid Paed 60/60). Products included in the tender that may be used in children and/or adults include isoniazid 100 mg and rifampicin 150 mg + isoniazid 75 mg (2FDC); majority of use assumed to be adult. The tender did not include additional medicines often used to treat paediatric TB (e.g. rifampicin 60 mg + isoniazid 30 mg + pyrazinamide 150 mg [3FDC], pyrazinamide 400 mg; rifampicin 60 mg + isoniazid 30 mg [2FDC]).

6.5. Market shortcomings

As part of the recently published 2013–2016 UNITAID Strategy, a Market Dynamics dashboard was developed to provide an overview of current market dynamics, including severity of market shortcomings related to availability, affordability, quality, acceptability/adaptability, and delivery. Market shortcomings related to TB medicines are especially pronounced for MDR-TB and paediatric medicines, as described below. Many are driven by the common theme of market fragmentation, highlighted in section 6.1.

6.5.1. Market shortcomings related to MDR-TB medicines

Availability: MDR-TB regimens are complex, expensive, long (20–24 months, including 8 months of injections), and can cause severe side-effects. (9) *Reasons*: Market incentives are limited: second-line drugs target a small population (diminished further by underdiagnosis), with little return on investment. Although some second-line drugs allow for visibility on and predictability of demand, drug resistance continues to evolve, making new drug development in some cases high risk. The typical approach to TB drug development—one medicine at a time—means that development of entirely novel regimens is long and challenging.[36]

Affordability: Although increased competition in moxifloxacin and cycloserine production has lowered the overall cost of regimens, the price of QA MDR-TB drugs remains prohibitively high (e.g. US$ 1800–6,000 + per treatment course[37] for a standard 24-month regimen, including 8 months of injectable capreomycin). (4, 23) *Reasons*: Increased manufacturing costs, low total volumes and unpredictable demand can be driven by complex production (e.g. for drugs requiring sterile fermentation), quality assurance requirements, low total volumes and market fragmentation from variable tender requirements by purchaser. Competition is limited: few suppliers exist for finished products and active ingredients of some key products. Prices have increased following manufacturer exit or lower than expected volumes (e.g. capreomycin; cycloserine) and product shortages (e.g. kanamycin). (23) Moxifloxacin remains under patent in some countries for select formulations, prohibiting generic manufacture. (23)[38]

Quality: QA medicines make up only part of the total market for MDR-TB medicines: a recent publication estimated that GDF procurement accounts for 31.7 % of all reported MDR-TB cases, or 4.2 % of estimated cases (by volume).[39] (85) TB medicines purchased by the private sector or NTPs are often of variable or unknown quality. *Reasons*: A small QA market limits incentives for producers to invest in stringent regulatory approval. Procurement by the private-sector programmes or NTPs may prioritize lowest price or domestic production over quality assurance.

Acceptability/adaptability: Current TB regimens are long (20–24 months for MDR TB), increasing treatment costs and decreasing adherence. *Reasons*: There are limited incentives for developers to invest in clinical trials for new TB medicines: the existing first-line regimen is high volume but cheap, while MDR-TB treatment is expensive but low volume.

Delivery: Low uptake of MDR-TB drugs: < 20 % of estimated cases receives appropriate treatment. (9) *Reasons*: Low availability of DST—about 5 % of patients (new, bacteriologically-positive cases) had access in 2012 (9)—means few MDR-TB cases are detected or treated appropriately. MDR-TB treatment is long, burdensome, expensive and prone to supply interruptions—reducing adherence and willingness to initiate treatment. National treatment programmes focus on first-line treatment and, as a result, often provide limited diagnosis or treatment for MDR TB.

Delivery: TB medicines are prone to supply shortages and stock-outs; prequalified products have long and variable lead times (tracked by GDF, with web-based live reports available). *Reasons*: Limited number of

---

36 Exceptions to this development approach include the TB Alliance and the Critical Path to TB Drug Regimens (CPTR); an initiative that is trying to address the issue of single drug development by encouraging, coordinating and facilitating the development of multidrug regimens.

37 Relative to capreomycin-containing regimens, potential for cost savings with kanamycin-containing regimens.

38 Initial pricing indications for bedaquiline, a new MDR-TB medicine, suggest that affordability will continue to be an issue. Further data on use and duration of treatment (refer to section 5) are needed to inform price and placement in therapy.

39 Further analysis of the GDF evolving role in procuring TB medicines has been conducted, with publications forthcoming. Meanwhile, GDF procurement (reported to be 39 383 MDR-TB treatment courses in 2012) accounted for approximately 47% of all reported MDR-TB cases (87 715), or about 9% of estimated new cases (450 000).

suppliers exist, especially of QA APIs. Lack of reliable, transparent forecasting of MDR-TB treatment numbers—in part due to difficulty in predicting speed of scale-up of DST—leads to low and variable demand, driving "made-to-order" production.

Delivery: Inappropriate medicine selection and use in the private sector. **Reasons**: Inappropriate prescribing by private-sector physicians can occur, partly due to the lack of enforced quality standards and lack of access to a full range of MDR-TB medicines in the private sector.

6.5.2. Market shortcomings related to paediatric TB medicines

Affordability: Paediatric TB medicines are more expensive than adult formulations: a 6-month course of QA, first-line TB drugs costs 40% more (US$ 22 for adults compared to US$ 30 for children) (4, 28), despite containing less active ingredient. **Reasons**: Few suppliers exist for QA formulations. A small market and fragmented demand increases risk for manufacturers, as do higher costs in product development (e.g. formulation; dosing; safety).

Quality: Fewer than one in five children with TB received QA drugs via GDF in 2012 (28), meaning many children are receiving drugs of unknown quality in non-standard doses (e.g. split adult FDC). **Reasons**: No appropriately dosed FDC is currently on the market (i.e. an FDC that corresponds to the dosing recommendations in the 2014 guideline update). A majority of the market is served by private-sector and non-donor public-sector TB drugs procurement, which is typically non-QA.

Acceptability/adaptability: No appropriately dosed, QA, paediatric FDC on the market consistent with 2014 WHO treatment guideline revision. Delays in needed paediatric trials for novel medicines (an average ≥7-year lag between adult and paediatric formulations, despite requirement for submission of plan for paediatric development). In second-line drugs, only amikacin, levofloxacin and linezolid have been developed for children, but even these are often not widely available or are for non-TB indications. (23) **Reasons**: The small, fragmented QA paediatric market is unattractive to developers (i.e. low return on investment due to very limited demand). Additional costs of product development and uncertain regulatory and quality requirements increase the risk of participating in this market.

Delivery: Paediatric TB medicines are prone to supply shortages and stock-outs; prequalified products can have a long lead time. **Reasons**: There is a limited number of QA finished product and active ingredient suppliers. Lack of reliable forecasting and low and variable demand contribute to made-to-order production.

TB diagnostics are not appropriate for children: 90% of children with TB is smear negative, and specimen collection in children is challenging (refer to Box 6). **Reasons**: Smear microscopy is not suited for children because: it requires sputum, which is difficult to collect; children have low levels of bacteria in sputum; and children are prone to extrapulmonary TB.

6.6. Potential opportunities for market intervention

6.6.1. Potential opportunities for market intervention: DS- and MDR-TB medicines

As described above, TB medicines markets are complex, fragmented and subject to a wide range of market shortcomings. These characteristics make design of market-based interventions challenging. Multiple or stepwise approaches may be appropriate for UNITAID and other stakeholders to consider. Given close links between market segments (e.g. APIs and finished pharmaceutical products; diagnostics and medicines), interventions are often interdependent. In addition, UNITAID recognizes the importance of a diverse range of stakeholders, including non-donor procurers of TB medicines, as patients seek care both in programmes funded by country governments and in the private sector. Complementary approaches and careful coordination between partners are, therefore, key to success.

As described in Box 3, the UNITAID 2013 Tuberculosis Market Forum explored potential opportunities for market-based intervention in TB markets. Key themes included work to:

- generate evidence to improve and simplify MDR-TB treatment and consolidate demand;
- support effective forecasting, procurement and supply management;
- facilitate healthy markets for TB API and finished pharmaceutical products;
- support coordination of donor and non-donor actors, including the private sector and government.

Generate evidence to improve and simplify MDR-TB treatment and consolidate demand

As illustrated in Figure 8, a wide range of treatment options exists even within current WHO-recommended regimens, particularly for MDR TB. While some of this variation is necessary, consolidation of the market around fewer, priority treatment regimens could improve market dynamics. First, additional clinical data are needed to inform drug choices and identify priority TB medicines and/or regimens around which to focus the market (see Box 4 for information on endTB, a UNITAID-funded project already planned in this area). Then, further interventions to improve market function may be possible—for example, engaging manufacturers of priority medicines to ensure reliable supply or secure and sustainable price agreements. Finally, "non-essential" variation unlinked to clinical needs (e.g. interchangeable packaging options or dosage forms) could be addressed. For example, inventory and review of current quality, regulatory, patent and tender processes, standards and requirements may identify opportunities to streamline or rationalize duplicates; simplify forecasting, supply chain management and scale-up; and improve market efficiency.

As noted in section 6.1, longer-term considerations follow market interventions in this area. For example, while streamlining product options for an already very small market could improve market dynamics, even fewer manufacturers may be required to meet demand. Close coordination between partners and over time is, therefore, required to optimize market dynamics.

Market guidance could stimulate and focus further innovation and speed the development of new treatment options. However, new medicines or regimens may become commercially available on the basis of limited data (e.g. accelerated or conditional approval following promising Phase II trial results), and uncertainty may remain regarding effectiveness, safety and potential drug–drug interactions with other medicines used for TB or co-infections, including HIV. Market approaches designed to accelerate scale-up and increase access to new drugs or regimens may be needed to manage this uncertainty and ensure appropriate access (e.g. built-in incentives for appropriate use; means to generate data to assess risk). Foundational work on intellectual property may be required to inform potential interventions to increase access to consolidated regimens containing drugs still under patent. Market approaches for "repurposed" medicines—including some already used for TB, even without a formal indication in TB—may also leverage opportunities such as untapped potential for increased generic competition.

Potential market-based approaches may include work to:

- generate data to simplify and standardize treatment regimens, informing choices within drug classes or regimen composition to consolidate demand within the MDR-TB market for new and existing drugs;
- identify and reduce non-essential variation—including redundant packaging options (e.g. an identical product is available in a blister pack or jar) and unnecessary dosage forms (e.g. an identical product is available in reconstituted and powder forms);
- support early determination of target product profiles, including price, for treatment regimens and related diagnostic tests and algorithms;
- model costs and impacts of new regimens and related diagnostic tools to better define potential future markets (e.g. better understand the market-consolidating potential of new regimens to dramatically simplify TB treatment).

Support effective forecasting, procurement and supply management[40]
Low, variable and uncertain demand can drive inefficient, made-to-order production, particularly for low-margin APIs. Demand forecasting to improve visibility on orders could stabilize the market—e.g. by encouraging manufacturers to produce API prior to orders being placed, or by facilitating competition among finished pharmaceutical product manufacturers. Forecasting efforts should be designed to provide realistic (versus aspirational) estimates, accounting for available funding, country capacity and other factors influencing demand. Market approaches may include mechanisms such as advanced commitments to assure forecasts, or other tools to link in-country supply chain efforts with forecasts.

Development of accurate forecasts for MDR-TB medicines is challenging. As described in section 6.1, small markets can be fragmented by multiple procurement channels—each with specific quality or regulatory standards and tender requirements. Many products of unknown quality are available, threatening the sustainability of markets for QA drugs. Supply issues can also be complicated by the fact that several TB medicines do not have an indication for TB. This may raise barriers to procurement or import, hinder the generation of demand and undermine incentives for generics to enter the market.

Furthermore, procurement channels are often complex, financing for products is uncertain and payment arrangements can be inflexible. These factors may hinder timely and appropriate ordering. For example, the requirement for up-front payments for expensive MDR-TB medicines represents a barrier for many countries. Funding can also be uncertain as donors' funding structure or requirements evolve. This complexity and uncertainty erode manufacturers' incentives to participate in the market and countries' ability to support strong, cost-effective procurement.

Market-based approaches that address forecasting, procurement and supply management issues could reduce the likelihood of shortages or stock-outs and improve access to lower-cost, QA products. Potential interventions in this area may include work to:

- improve quantification through introduction of monitoring tools and systems, consolidation of demand and support for forecasting and order planning—where complementary mechanisms may include strategic stockpiles[41] and/or advanced purchase commitments;
- increase demand for QA products (e.g. demand incentives; technical support for manufacturers seeking prequalification; harmonization of regulatory/evidence requirements; work with private insurance schemes or innovative business models);
- stabilize procurement and ensure timely payment to stabilize supply—where mechanisms may include a flexible procurement fund to reduce payment delays and consolidate volume and/or support for more transparent tendering processes.[42]

---

40 Note: As donor-funded purchases make up only part of the global market for TB medicines, there are limitations to some of the market interventions described here: some may optimize only a segment of the global market; some may be more relevant for non-donor stakeholders or be especially dependent on coordination for global impact.
41 For example, the use of GDF donor-funded (USAID and UNITAID) stockpile for decreasing lead times and enabling market consolidation.
42 GDF, for instance, with the help of USAID funding, set up a flexible fund of US$ 4.8 million that allows countries to use funds as a guarantee for all direct procurement. This will help countries to place orders on time and avoid treatment interruption.

Facilitate healthy markets for TB API and finished pharmaceutical products

Many potential manufacturers of MDR-TB API and finished product choose not to participate in this high-risk market—given its small size, fragmented nature and high uncertainty (see Box 5). As a result, near-monopolies exist for some products, especially those with complex manufacturing processes and low profit margins. Poor quantification and forecasting, as discussed above, often leads to suboptimal small-batch production, especially for MDR-TB medicines. As described in section 6.3.3, technology transfer or production capacity issues have impacted the availability or price of capreomycin, PAS sodium and kanamycin. Product-specific interventions to reduce barriers to entry can encourage greater competition, stimulating price reductions and expanded access, especially where the potential of generics has not been fully realized.

The API market is particularly low margin and sensitive to economies of scale. This may mean that API markets can support fewer manufacturers. Similarly, the economics of markets for very low-volume products (such as many MDR-TB medicines) may be different from higher volume products because of the need to combine many orders to reach a minimum batch size to produce products efficiently. These very low-volume markets also may support only a small number of manufacturers.

The primary focus of interventions in markets that can support only few manufacturers may be to stabilize supply. Where a market can sustain more manufacturers, different market interventions may be possible to increase competition and reduce prices. As API and finished pharmaceutical products are closely linked, the correct sequencing of market interventions in this area is critical to avoid unintended disruption of other market segments, and to ensure that gains in API markets translate to beneficial market and public health impact.

Potential market-based approaches may include work to:

- stabilize API markets for TB medicines—e.g. by increasing production efficiency through manufacturing improvements (process chemistry changes, production or scale efficiencies); or by increasing availability of QA API through technical assistance and/or incentives such as advanced purchase commitments;

- increase competitiveness of finished product markets for TB medicines—e.g. by increasing incentives for additional QA finished product manufacturers to enter the market to increase competition and drive prices down;

- support for regular and reliable procurement through mechanisms such as advanced purchase processes to increase volume, enable batch size optimization and smooth demand fluctuations (e.g. through stockpiles).

Improved market intelligence and an evolving understanding of API and finished product markets will be essential in informing potential market-based opportunities. This should include work to: map finished product to API sources to improve understanding of the interrelatedness of these markets; research production costs and processes, particularly of APIs; undertake modelling to define economies of scale and optimize competition for each API and finished product.[43]

Support coordination of donor and non-donor actors, including the private sector and government

As described in section 6.1 and illustrated in Figure 6 and Figure 7, key high-burden countries finance significant TB medicines procurement (especially BRICS and other middle-income countries). In addition, many patients seek TB care from private-sector care providers. As such, donors' leverage as the primary funders of TB medicines procurement is limited in TB, and coordination with other stakeholders is essential.

This presents challenges, however. While significant (thought to be up to 50–80% in some countries), the private sector is largely unregulated. Private providers may use inappropriate tests and regimens, procure drugs from different manufacturers and through different channels from the public sector, and use non-QA drugs and diagnostics. On the other hand, care by some practitioners in the private sector can be as good as or, in some cases, better than the public sector. In this complex environment, market interventions that

---

43 Work to improve market intelligence on API markets is under way, including UNITAID support for the William Davidson Institute.

effectively engage country procurers and the private sector could facilitate broader access to appropriate, affordable, QA TB medicines.

Potential market-based approaches may include work to:

- engage non-donor stakeholders in innovative, sustainable and scaleable ways—e.g. using social business models, financial and other incentives to improve access to appropriate medicines;
- support coordination of procurement with public sector—e.g. encouraging combined public- and private-sector reporting and quantification for better market transparency and purchasing power.

A better understanding of patient pathways may be needed to inform market-based interventions that engage non-donor stakeholders. That is, a mapping of where patients seek care first and how their care progresses could inform effective private-sector interventions that optimize patient outcomes. Furthermore, additional information is needed to best define leverage points to define incentives to most effectively engage private-sector care providers.

6.6.2. Potential opportunities for market intervention: paediatric TB medicines

UNITAID currently funds the TB Alliance to: map the paediatric market; develop and deliver new appropriately dosed, QA, fixed-dose TB medicines for children; and drive policy and regulatory change to scale up treatment and accelerate availability of paediatric formulations of new and emerging TB medicines and regimens. Meanwhile, UNITAID remains committed to supporting treatment of children with TB through its extended engagement with GDF, and is open to other, complementary market interventions in this space.

Potential opportunities related to the paediatric TB medicines market may include interventions to:

- Consolidate demand, negotiate prices and scale up QA medicines. *(NB: this is most relevant once new QA, paediatric formulations are available, expected by 2016)*.
- Incentivize development and facilitate uptake of novel TB diagnostics appropriate for children.[44] Given the significant challenge of underdiagnosis in children (see section 4.2 and Box 6), better diagnosis is a necessary precursor to improved access to paediatric TB medicines. Possible opportunities may include: scale-up of currently available technology where appropriate for children; scale-up with alternate specimen types; and support to establish evidence for paediatric TB with new technologies.

---

44 Refer to UNITAID 2014 Tuberculosis Diagnostic Technology and Market Landscape, 3rd edition (forthcoming publication).

Appendix 1. Additional detail on methods for select figures and sections

Figure 3. Global estimates of paediatric TB medicines need, demand and access

Sources and notes: 530 000 estimated incident TB cases in children in 2012 by WHO; assumes ratio of notified to incident cases (66%) is the same for adults and children. (9) A recent mathematical model estimates a total of roughly 650 000 paediatric TB cases in high-burden countries; extrapolation suggests a global total of up to approximately 813 000. (26) Other recent studies estimate that the global caseload could be as high as 1 million, reflected in the chart. (24) There were 349 000 total childhood notifications in 2012: this includes reported paediatric cases and an estimate of the number of paediatric cases in countries that did not report notifications disaggregated by age. (9) There were 242 000 and 117 000 paediatric TB treatments procured by GDF in 2010 and 2011, respectively. There were 74 000 deaths from TB among HIV-negative children in 2012, (9) but deaths from TB among HIV-positive children are classified as HIV-related deaths.

Figure 6. Value of the 2012 first-line TB medicines market, by procurement channel (US$ millions)

Sources and notes: Total market approximated from build-up of various procurement channels, estimated as follows. **PPM**: Derived estimates of the portion of the private market treated through PPM programmes (versus unregulated private sector) from analysis of limited available data from literature, as follows. Calculated number of patients accessing TB treatment in the private sector for 22 high-burden countries as: [estimated incident cases (2012) (9)] x [% of patients accessing TB treatment in the private sector (86)]. Interpreted estimates of PPM coverage (as % of private sector) with country-specific assumptions: China: PPM known to be extensive, but not quantified; assumed 80%. Democratic Republic of the Congo: PPM coverage unknown - assumed negligible, as no patients access TB care from private sector. Indonesia, Thailand: assumed % of patients treated in PPM = % of private physicians engaged with PPM. Mozambique: PPM coverage known to be minimal (five physicians only), but not quantified; assumed negligible. Nigeria, South Africa: PPM coverage unknown; calculations reflect possibility that 0–100% of private sector may be engaged with PPM programmes. United Republic of Tanzania: PPM coverage known to be minimal (12 physicians only), but not quantified; assumed negligible. **Private**: estimated total private market volumes by extrapolating total number of patient treatments procured in private sector from literature (86), adjusted for country-specific burden of disease. (9) Applied estimates of PPM coverage (as % of private sector) to estimate range of patient treatments procured through PPM programmes versus unregulated private sector. Extrapolated from 22 high-burden countries to global totals based on ratio of estimated incident cases. Multiplied number of patients by assumed typical cost of treatment regimen (US$ 40) to size PPM and unregulated/uncertain market segments by value. Chart reflects midpoint of value estimate for PPM market segment (US$ 20 million); and balance of overall total private market (US$ 205 million) as unregulated/uncertain. Approaches assume market structure has been stable since 2008 coverage estimates, and that notified cases represent the total market (i.e. number of patients treated, but not notified is negligible). **Donor**: extrapolation of data reported in Global Fund PQR; Global Fund share of total donor market from WHO Global Tuberculosis Report 2012. (1) **Public non-donor**: extrapolation of data reported to WHO from 99 countries accounting for 85% of global DS-TB cases receiving treatment; (1) for South Africa only, used actual tender data (50% of two-year tender for TB medicines, covering from 1 August 2013 to 31 July 2015). **South Africa**: analysis of bids HP01-2013TB, HP02-2013AI and HP01-2013TB/01; supply and delivery of anti-tuberculosis medicines to the Department of Health for the period from 1 August 2013 to 31 July 2015. (2, 3, 119) Tender document HP01-2013TB/01 includes estimates for streptomycin (180 thousand x 3 ml injection vials, 1 g/3 ml), but no pricing or value data; this product is not included in value calculations. Used exchange rate as of 6 August 2013 (date contract signed): 9.91414 ZAR = US$ 1. (101) Assumed 50% of tender would roughly approximate 2013 value of TB medicines. **India**: Analysis of Indian government purchases of TB medicines in fiscal year 2010–2011; data and interpretation by Access Health International for UNITAID. Data reflect procurement through RITES with Indian government funds, including World Bank loans, but excluding GDF procurement with donor funds. (5) **GDF**: data from 2012 Annual Report. (92)

Figure 7. Value of the 2012 MDR-TB medicines market, by procurement channel (US$ millions)

Sources and notes: WHO estimated a total 2012 market of over US$ 300 million for MDR-TB medicines. (9) Total market approximated from build-up of various procurement channels, estimated as follows. **Private**: US$ 37 million in private-sector sales were reported for five countries only in 2007; (86) assumed additional US$ 35 million private sector worldwide based on global market estimates of US$ 300 million for all MDR-TB medicines, less value of donor and public segments. **Donor**: extrapolation of data reported in Global Fund PQR; Global Fund share of total donor market from WHO Global Tuberculosis Report 2012. (1) **Public non-donor**: extrapolation of data reported to WHO from 99 countries accounting for 29% of MDR-TB cases receiving treatment; (1) for South Africa only, used actual tender data (50% of two-year tender for TB medicines, covering for the period from 1 August 2013 to 31 July 2015). **South Africa**: analysis of bids HP01-2013TB, HP02-2013AI and HP01-2013TB/01; supply and delivery of anti-tuberculosis medicines to the Department of Health for the period 1 August 2013 to 31 July 2015. (2, 3, 119) (Tender document HP01-2013TB/01 includes (apparently unfulfilled) estimates for levofloxacin (5 million x 250 mg tablets + 420 thousand x 750 mg tablets); linezolid (400 thousand x 600 mg tablets + 150 vials x 20 mg/ml granules for suspension); and moxifloxacin (9 million x 400 mg tablets); these products are not included in value calculations. Used exchange rate as of 6 August 2013 (date contract signed): 9.91414 ZAR = US$ 1 (x-rates. com). Assumed 50% of tender would roughly approximate 2013 value of TB medicines. **India**: analysis of Indian government purchases of TB medicines in fiscal year 2010–2011; data and interpretation by Access Health International for UNITAID. Data reflect procurement through RITES with Indian government funds, including World Bank loans, but excluding GDF procurement with donor funds. (5) NB: Revised National TB Control Programme annual report cited second-line TB medicines expenditure at 22% of budget; with a 2011–2012 budget of US$ 73.6 million (400.00 rupees in crore), this amounts to US$ 16.2 million, but may include medicines funded by the Global Fund. **GDF**: data from 2012 Annual Report. (92) 2012 data, while not consistently available across all channels, show that GDF procurement of MDR-TB medicines increased by over 50% from 2011 to 2012. (85)

Calculations referenced in section 6.2.3

Calculated prices of product PC-1, kit containing medicines for two months of intensive-phase treatment, followed by four months of continuation-phase treatment: 24 combi-packs of (2x isoniazid 300 mg tablets, 1x rifampicin 450 mg capsule, 2x pyrazinamide 750 mg tablets and 2x ethambutol 600 mg tablets) in one pouch and 18 multiblister calendar combi-packs of Schedule-2 (6x isoniazid 300 mg tablets, 3x rifampicin 450 mg capsule and 4x pyridoxine 5 mg tablets) in another pouch.

Calculations referenced in section 6.3.3

Product-specific median costs were calculated in Tableau by transaction rather than by unit. Separately, a manual calculation was done to determine the median by number of units for all products where this information was available. The two methods did not produce significant discrepancies in most cases, and for all products, market trends and associated narrative description based on median costs by transaction (as described in section 6.3.3) were unaffected. For consistency, median costs by transaction have, therefore, been retained for all products in this edition of the landscape. Where deviations in results from the two methods were apparent, these were noted where relevant in the source and notes of the applicable figure.

Calculations referenced in section 6.4.3

GDF prices from online catalogue. (4) South African government prices derived from analysis of South African tender data: bid HP01-2013TB and bid HP01-2013TB/01, supply and delivery of anti-tuberculosis medicines to the Department of Health for the period from 1 August 2013 to 31 July 2015. (2, 3) Used exchange rate as of 6 August 2013 (date first contract signed): 9.9141 ZAR = US$ 1. (13) VAT for delivered prices reported in South African tender data = 14%; excluded in figures cited.

Appendix 2. Quality assurance of TB medicines

Table A 1. Availability of QA formulations of key first-line TB medicines

Drug	Formulation	Strength	WHO PQ options	SRA-approved options	ERP options	Total QA options
isoniazid (H)	tablet	300 mg	3	3	3	7
rifampicin (R)	capsule[a]	150 mg	1	3	0	4
		300 mg	1	2	0	3
pyrazinamide (Z)	tablet/capsule	250 mg	0	0	0	0
		400 mg	3	0	1	3
		500 mg	3	4	1	7[b]
ethambutol (E)	coated tablet/ capsule	200 mg	0	0	1	1
		275 mg	0	0	0	0
		400 mg	0	2	0	2[c]
streptomycin	powder for injection (vial)	1 g	0	4	0	4
		0.75 g	0	0	0	0
isoniazid+rifampicin (HR)	coated tablet/ capsule	75 mg/150 mg	5	0	5	6
		150 mg/150 mg	1	0	1	1
		150 mg/300 mg	0	2	0	2[d]
isoniazid+ethambutol (HE)	coated tablet	150 mg/400 mg	3	0	3	4
isoniazid+rifampicin+ethambutol (HRE)	coated tablet	75 mg/150 mg/275 mg	3	0	2	3
isoniazid+rifampicin+ pyrazinamide (HRZ)	coated tablet/ capsule	150 mg/150 mg/500 mg	0	0	0	0
		75 mg/150 mg/400 mg	0	0	0	0
isoniazid+rifampicin+ pyrazinamide+ethambutol (HRZE)	coated tablet	75 mg/150 mg/400 mg/ 275 mg	5	0	3	5

[a] Table reflects capsule options only; also available as 150 mg film coated tablet (one SRA-approved option), 300 mg film coated tablet (one SRA-approved option) and 100 mg/5 ml granule for syrup (two SRA-approved options).
[b] Table reflects regular tablets only; also available as film-coated tablets (one SRA-approved option).
[c] Table reflects film-coated tablets only; also available as tablets (four WHO PQ options, three ERP options, five SRA options).
[d] Table reflects film-coated tablets only; also available as tablet (one SRA-approved option and one ERP-approved option) and as capsule (one WHO PQ option and one SRA-approved option).

Sources and notes: List derived from Drugs@FDA Database (114), WHO list of prequalified medicines (120), and lists of A, B and ERP-reviewed products. (121) ERP: Expert Review Panel, hosted by WHO on behalf of the Global Fund; QA: quality-assured; SRA: stringent regulatory authority. Refer to Box 2 for additional context.

Table A 2. Availability of QA formulations of key MDR-TB medicines

Drug	Formulation	Strength	WHO PQ options	SRA-approved options	ERP options	Total QA options
amikacin	solution for injection	500 mg/2 g vial	2	4	0	6
	powder for injection	1 g vial	0	0	0	0
capreomycin	powder for injection	1 g vial	0	3	0	3
cycloserine	capsule	250 mg	4	1	2	7
ethionamide	tablet/capsule	250 mg	4	1	2	5
kanamycin	powder for injection[a]	1 g vial	0	1	0	1
		500 mg vial	0	0	0	0
levofloxacin	tablet/capsule	250 mg	3	17	3	20[b]
	tablet	500 mg	3	17	3	20[c]
		750 mg	1	15	1	16[d]
moxifloxacin	tablet/capsule	400 mg	3	5	3	10[e]
ofloxacin	tablet/capsule	200 mg	3	2	3	6
		400 mg	2	2	3	5
prothionamide	tablet/capsule	250 mg	1	2	3	5
PAS	sachets, granules	4 g	0	1	0	1
PAS sodium	jar, granules	100 g	0	0	0	0
	sachet, granules	5.52 g	1	1	0	1
		9.2 g	1	0	0	1
terizidone	tablet/capsule	250 mg	0	1	0	1
		300 mg	0	0	0	0

[a] Also available as solution for injection (three SRA-approved options in different concentrations).
[b] For 250 mg tablet, there are two more options available with tentative approval status from the US FDA.
[c] For 500 mg tablet, there are two more options available with tentative approval status from US FDA.
[d] For 750 mg tablet, there are two more options available with tentative approval status from the US FDA.
[e] Multiple SRA-approved registrations from Bayer (e.g. prior to centralized EMA registration); considered as one product.

Sources and notes: List derived from Drugs@FDA Database (114), WHO list of prequalified medicines (120), and lists of A, B and ERP-reviewed products. (121) ERP: Expert Review Panel, hosted by WHO on behalf of the Global Fund; QA: quality-assured; SRA: stringent regulatory authority.

Appendix 3: TB medicines procurement channels related to GDF

Figure A 1. TB medicines procurement channels related to GDF, with supplementary detail
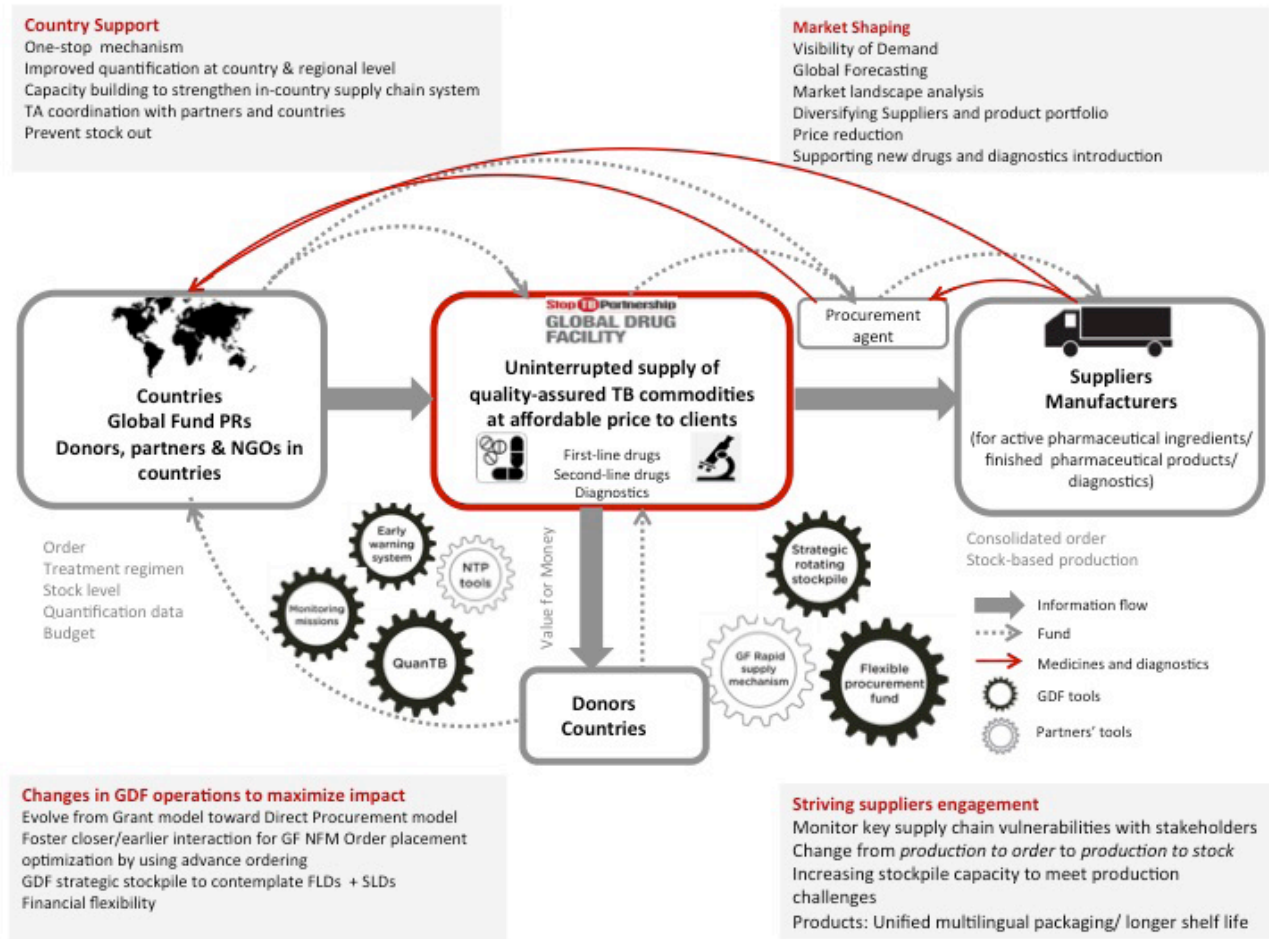
Sources and notes: Reprinted with permission of GDF. (82) Illustration provides supplementary information to Figure 1, TB medicines procurement channels cited in this report.

References

1. Global tuberculosis report. Geneva: World Health Organization; 2012.

2. Department of Health. Contract: HP01-2013TB: supply and delivery of anti-tuberculosis medicines to the Department of Health for the period 1 August 2013 to 31 July 2015. Pretoria: Republic of South Africa; 2013.

3. Department of Health. Contract: HP01-2013TB/1: supply and delivery of anti-tuberculosis medicines to the Department of Health for the period up to 31 July 2015. Pretoria: Republic of South Africa; 2013.

4. Global Drug Facility offers PASER without the need for cold chain storage. Geneva: Stop TB Partnership; 2014 (http://www.stoptb.org/news/announcements/2014/a14_015.asp, accessed 14 July 2014).

5. Tuberculosis medicines—India market analysis (unpublished); procurement data obtained through RTI applications filed with Central TB Division and RITES for the project. Hyderabad: Access Health International; 2013.

6. Global Drug Facility annual report. Geneva: Stop TB Partnership; 2011.

7. National Institutes of Allergy and Infectious Disease. Tuberculosis (TB). Washington DC: United States Department of Health and Human Services, National Institutes of Health; 2012 (http://www.niad.nih.gov/topics/tuberculosis/understanding/pages/treatment.aspx).

8. WHO Tuberculosis fact sheet No. 334. Geneva: World Health Organization; 2013 (http://www.who.int/mediacentre/factsheets/fs104/en/index.html, accessed 14 March 2014).

9. Global tuberculosis report. Geneva: World Health Organization; 2013.

10. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011.

11. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis. 2010;50(Suppl. 3):S201–S207.

12. WHO calls tuberculosis a global emergency. Geneva: World Health Organization; 24 April 1993.

13. Global strategy and targets for tuberculosis prevention, care and control after 2015, 1st edition. Geneva: World Health Organization; 2014 (http://www.who.int/tb/post2015_tbstrategy.pdf?ua = 1, accessed 9 June 2014).

14. Phillips L. Infectious disease: TB's revenge. Nature. 2013;493(7430):14–16.

15. Pawlowski A, Jansson M, Skold M, Rottenberg ME, Kallenius G. Tuberculosis and HIV co-infection. PLoS Pathog. 2012;8(2):e1002464.

16. 2010/2011 Tuberculosis global facts. Geneva: World Health Organization; 2011 (http://www.who.int/tb/piblications/2010/factsheet_tb_2010.pdf, accessed 10 March 2014).

17. Gandhi NR et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368(9547):1575–80.

18. The Global Plan to Stop TB 2011–2015. Geneva: World Health Organization; 2010.

19. Multi-drug resistant tuberculosis: update [slide deck]. Geneva: World Health Organization; 2013.

20. Marais BJ. Quantifying the tuberculosis disease burden in children. Lancet. 2014;383(9928):1530–1.

21. Steingart K, Schiller I, Horne D, Pai M, Boehme C, Dendukuri N. Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane Collaboration. 2014(1):1–44.

22. Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. Geneva: World Health Organization; 2013.

23. DR-TB drugs under the microscope, 3rd edition. Geneva: Médecins sans Frontières; October 2013.

24. Jenkins HE et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572–9.

25. Detjen A, Mace C, Perrin C, Graham S, Grzemska M. A survey of the adoption of revised dosage recommendations for childhood tuberculosis in countries with different childhood TB burden. Public Health Action. 2012:126–32.

26. Dodd P, Gardiner E, Coghlan R, Seddon J. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. The Lancet Global Health, Early Online Publication, 9 July 2014.

27. Scott C, Gardiner E, de Lucia A, Keravec J. Distribution of First-line pediatric drugs in 22 HBCs: analysis of Global Drug Facility procurement. Unpublished analysis. Geneva: TB Alliance and GDF; 2013.

28. Distribution of first line pediatric drugs from 22 HBCs: analysis of Global Drug Facility procurement. Geneva: TB Alliance and GDF; 2013. Unpublished data.

29. Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(6):449–56.

30. Treatment of tuberculosis guidelines, 4th edition. Geneva: World Health Organization, Stop TB Department; 2009.

31. Guidelines for the programmatic management of drug-resistant tuberculosis update. Geneva: World Health Organization; 2011.

32. The use of short regimens for treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization; 2012 (http://www.who.int/tb/challenges/mdr/short_regimen_use/en/).

33. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization; 2006.

34. Rapid advice: treatment of tuberculosis in children. Geneva: World Health Organization; 2010 (http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf).

35. Guidelines for national tuberculosis programmes on the management of tuberculosis in children, 2nd edition. Geneva: World Health Organization; 2014.

36. International Union Against Tuberculosis and Lung Disease. Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children recommendations for a public health approach. Geneva: World Health Organization, 2010.

37. WHO policy on collaborative TB/HIV activities guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012.

38. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. Atlanta: Centers for Disease Control and Prevention; 2011 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm).

39. Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst. Rev. 2013;7:Cd007545.

40. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annu Rev Public Health. 2013;34:271–86.

41. The PIH guide to the medical management of multidrug-resistant tuberculosis, 2nd edition. Boston: USAID TB CARE II, Partners In Health; 2013.

42. Latent tuberculosis infection: a guide for primary health care providers. Atlanta: Centers for Disease Control and Prevention; 2014 (http://www.cdc.gov/tb/publications/ltbi/treatment.htm).

43. Gospodarevskaya E et al. Patient costs during tuberculosis treatment in Bangladesh and Tanzania: the potential of shorter regimens. Int J Tuberc Lung Dis. 2014;18(7):810–17.

44. Abu-Raddad LJ et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proc Natl Acad Sci U S A. 2009;106(33):13980–5.

45. Sterling T et al. Three months of weekly rifapentine and isoniazid for M. tuberculosis infection in HIV-infected persons (Poster 817). Poster session presented at the Conference on Retroviruses and Opportunistic Infections, Boston, 5 March 2014.

46. Podany A BY, Chaisson R. Efavirenz pharmacokinetics in HIV + persons receiving rifapentine and isoniazid for TB prevention (Poster 105). Poster session presented at the Conference on Retroviruses and Opportunistic Infections, Boston, 5 March 2014.

47. CRAG, TAG welcome Sanofi U.S. commitment to reduce the price of tuberculosis drug rifapentine. Treatment Action Group; 2014 (http://www.treatmentactiongroup.org/tb/press/2013/crag-tag-welcome-sanofi-us-commitment-reduce-price-tuberculosis-drug-rifapentine).

48. Fofana MO, Knight GM, Gomez GB, White RG, Dowdy DW. Population-level impact of shorter-course regimens for tuberculosis: a model-based analysis. PLoS One. 2014;9(5):e96389.

49. Merle C FK, Lapujade O. A randomized controlled trial of a 4-month gatifloxacin-containing regimen vs. standard 6-month regimen for treating drug-susceptible pulmonary tuberculosis: main efficacy and safety results of the OFLOTUB trial. Paper presented at The 44th Union World Conference on Lung Health, Paris, 30 October–3 November 2013.

50. New tuberculosis drug regimen will move to landmark phase 3 clinical trial. Geneva: TB Alliance; 2014 (http://www.tballiance.org/newscenter/view-brief.php?id = 1096).

51. DR-TB drugs under the microscope. Médicins sans Frontières and the International Union Against Tuberculosis and Lung Disease; 2014 (http://www.msfaccess.org/our-work/overcoming-barriers-access/article/888).

52. Cox H et al. Rational use of moxifloxacin for tuberculosis treatment. Lancet Infect Dis. 2011;11(4):259–60.

53. Singh KP, Brown M, Murphy ME, Gillespie SH. Moxifloxacin for tuberculosis. Lancet Infect Dis. 2012;12(3):176; author reply 7–8.

54. Boeree M. The High Rif trials of the PanACEA Group. Presentation at the 44th The Union World Conference on Lung Health, Paris, 30 October–3 November 2013.

55. MAMS study has completed first interim analysis. PanACEA; 2014 (http://panacea-tb.net/mams-study-has-completed-first-interim-analysis, accessed 9 June 2014).

56. Mendel C. TB Alliance, New York, personal communication with Erica Lessem, Treatment Action Group, New York, 16 April 2014.

57. Diacon A et al. 14 day EBA study of PA-824, bedaquiline, pyrazinamide and clofazimine in smear-positive TB patients (Abstract 97LB). Presentation at the Conference on Retroviruses and Opportunistic Infections, Boston, 5 March 2014.

58. Ruiz Mingote L et al. The use of bedaquiline in regimens to treat drug-resistant and drug-susceptible tuberculosis: a perspective from TB-affected communities. Lancet. In press.

59. Van Deun A et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182(5):684–92.

60. Wells WA et al. Alignment of new tuberculosis drug regimens and drug susceptibility testing: a framework for action. Lancet Infect Dis. 2013;13(5):449–58.

61. Dheda K et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet. 2010;375(9728):1798–807.

62. Pietersen E et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014;383(9924):1230–9.

63. European Medicines Agency. Sirturo; 2014 (http://www.ema.europa.eu/ema/index.jsp?curl = pages/medicines/human/medicines/002614/human_med_001730.jsp&mid = WC0b01ac058001d124).

64. Anti-infective drugs advisory committee meeting briefing document TMC207 (bedaquiline). Treatment of patients with MDR-TB. NDA 204-384. United States Food and Drug Administration; 28 November 2012 (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf, accessed 9 June 2014).

65. Deltyba. European Medicines Agency; 2014 (http://www.ema.europa.eu/ema/index.jsp?curl = pages/medicines/human/medicines/002552/human_med_001699.jsp&mid = WC0b01ac058001d124, accessed 9 June 2014).

66. Gler M et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012(366).

67. Diacon AH et al. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrob Agents Chemother. 2010;54(8):3402–7.

68. Wallis RS et al. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. PLoS One. 2014;9(4):e94462.

69. McCance-Katz EF, Moody DE, Prathikanti S, Friedland G, Rainey PM. Rifampin, but not rifabutin, may produce opiate withdrawal in buprenorphine-maintained patients. Drug Alcohol Depend. 2011;118(2–3):326–34.

70. TB/HIV. World Health Organization; 2014 (http://www.who.int/tb/challenges/hiv/en, accessed 9 June 2014).

71. Global Drug Facility reaches a 58% price reduction for rifabutin by adding a new supplier to its product catalogue. Stop TB Partnership; 2014 (http://us3.campaign-archive2.com/?u = 85207b84f0f2d8ddc9bd878de&id = f81bd34c7e&e = d66fa71e94, accessed 9 June 2014).

72. Everitt D, Egizi E. Pharmacokinetic interaction between the investigational anti-tuberculosis agent TMC207 and rifampicin or rifapentine (Abstract MOAB0304). Paper presented at the 19th International AIDS Conference, Washington DC, 22–27 July 2012.

73. van Heeswijk R et al. The effect of nevirapine on the pharmacokinetics of TMC207, an investigational antimycobacterial agent (Abstract MOPE172). Paper presented at the 6th International AIDS Conference, Rome, 17–20 July 2011.

74. Dannemann B et al. Corrected QT interval prolongation in a phase 2 open-label trial of TMC207 plus background regimen as treatment for MDR-TB: effect of co-administration with clofazimine (Abstract A-1259). Paper presented at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 9–12 September 2012.

75. Svensson E et al. Population pharmacokinetics of bedaquiline (TMC207) and its M2 and M3 metabolites with efavirenz demonstrate reduced exposure. Paper presented at the 5th International Workshop on Clinical Pharmacology of TB Drugs, San Francisco, 8 September 2012.

76. Paccaly A et al. Absence of clinically relevant drug interaction between delamanid, a new drug for multidrug-resistant tuberculosis (MDR-TB) and tenofovir or lopinavir/ritonavir in health subjects (Poster Exhibition). 19th International AIDS Conference, Washington DC, 22–27 July 2012.

77. Dooley K. Trial of the safety and PK of the investigational anti-TB drug PA-824 co-administered with lopinavir/ritonavir or rifampin: ACTG Study A5306. 6th International Workshop on Clinical Pharmacology of TB Drugs, Denver, 9 September 2013.

78. Nguyen T et al. Evaluation of Xpert MTB/RIF and MODS assay for the diagnosis of pediatric tuberculosis. BMC Infect Dis. 2013;13(31).

79. Roadmap for childhood tuberculosis: toward zero deaths. Geneva: World Health Organization; 2013.

80. Wells WA et al. Size and usage patterns of private TB drug markets in the high burden countries. PLoS One. 2011;6(5):e18964.

81. Stop TB Partnership. Global Drug Facility annual report. Geneva: World Health Organization, 2013.

82. Stop TB Partnership. Global Drug Facility annual report 2012–2013. Geneva: World Health Organization, 2014.

83. Global malaria report. Geneva: World Health Organization; 2013.

84. Kates J, Wexler A, Lief E. Financing the response to HIV in low- and middle-income countries: international assistance from donor governments in 2013. UNAIDS and the Kasier Family Foundation; 2014.

85. Arinaminpathy N, Cordier-Lassalle T, Vijay A, Dye C. The Global Drug Facility and its role in the market for tuberculosis drugs. Lancet. 2013;382(9901):1373–9.

86. Wells W et al. Implications of the current tuberculosis treatment landscape for future regimen change. Int J Tuberc Lung Dis. 2011;15(6).

87. Pablos-Mendez A, editor. Leveraging the economic transition in health to improve private and public sector TB care. Washington DC: Public Private Mix (PPM) Models for the Sustainability of Successful TB Control Initiatives; May 2014.

88. Global Fund Quality Assurance Policy for Diagnostics. Global Fund to Fight AIDS, Tuberculosis and Malaria; 2011 (http://www.theglobalfund.org/en/procurement/quality/diagnostics, accessed 26 April 2013).

89. Access Campaign. Summary: DR-TB drugs under the microscope. Médicins sans Frontières; 2011 (http://www.doctorswithoutborders.org/publications/reports/2011/Report_Summary_DR-TB_Drugs_Under_the_Microscope.pdf, accessed 4 April 2013).

90. Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former soviet union. Malta: World Health Organization; 2011.

91. Bate R et al. Substandard and falsified anti-tuberculosis drugs: a preliminary field analysis. Int J Tuberc Lung Dis. 2013.

92. Stop TB Partnership. Global Drug Facility annual report. Geneva: World Health Organization, 2012.

93. Anand G, Shreya S, McKay B. Shortages of drugs threaten TB fight. Wall Street Journal. June 2013.

94. Meeting report: a silent crisis: tuberculosis drug shortages in the United States. Washington DC: PATH Offices; 18 January 2013.

95. Pathway to patients: charting the dynamics of the global TB drug market. New York: Global Alliance for TB Drug Development; 2007.

96. New hope for MDR-TB patients. Stop TB Partnership; 2014 (http://www.stoptb.org/webadmin/ cms/preview_n.asp?VID = 123, accessed 12 September 2014).

97. Yadav P. Analysis of the market structure, incentives and cost drivers of the API market for MDR-TB drugs. Ann Arbor: William Davidson Institute; 2012. Unpublished report.

98. TB online. Global Tuberculosis Community Advocacy Board; 2011 (http://www.tbonline.info/ posts/2011/8/23/capreomycin, accessed 24 May 2013.

99. Essential medicines for children: tuberculosis treatment in children. Geneva: World Health Organization; 2013 (updated 30 May) (http://www.who.int/childmedicines/tuberculosis/en/).

100. Richardson I. Interview with Iain Richardson. Indianapolis: Lilly Foundation; August 2013.

101. Prequalification Programme: a United Nations programme managed by the World Health Organization; 2014 (http://apps.who.int/prequal/default.htm, cited 21 July 2014).

102. Department of Health. Contract number HP01-2011TB/01: supply and delivery of anti-tuberculosis medicines to the Department of Health for period up to 31 July 2013 (Internet). Pretoria; Republic of South Africa; 2012 (http://www.doh.gov.za/docs/contracts/2012/hp01-2011tb_.pdf).

103. Smith L, Yadav P. Analysis of the Global Fund financed market for TB medicines: competitive landscape, market shares, product volumes and product variety. Ann Arbor: William Davidson Institute; January 2014.

104. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. Clin Infect Dis. 2010;50(Suppl. 3):S184–S194.

105. TB Alliance receives grant from UNITAID to develop pediatric TB drugs. Global Alliance for TB Drug Development; 2012 (http://www.tballiance.org/newscenter/view-brief.php?id = 1058, accessed 29 May 2013).

106. Graham S et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an Expert Panel. J Infect Dis. March 2012;205(Suppl. 1):S199–S208.

107. Cuevas L et al. Evaluation of tuberculosis diagnostics in children: 2. Methodological issues for conducting and reporting research evaluations of tuberculosis diagnostics for intrathoracic tuberculosis in children. Consensus from an Expert Panel. J Infect Dis. April 2012;205(Suppl. 2):S209–S215.

108. Moore H, Apolles P, de Villiers P, Zar H. Sputum induction for microbiological diagnosis of childhood pulmonary TB in a community setting. Int J Tuberc Lung Dis. 2011;15(9):1185–90.

109. Zar H et al. Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. Clin Inf Dis. 2012;55(8):1088–95.

110. Hillemann D, Rüsch-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary TB by the Automate GeneXpert MTB/RIF System. J Clin Microbiol. 2011;49:1202–5.

111. Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary TB? J Clin Microbiol. 2011;49(7):2540–5.

112. Nicol M et al. Accuracy of the Xpert MT/RIF test for the diagnosis of pulmonary TB in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infect Dis. 2011;11(11):819–24.

113. Sekkade M et al. Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary TB in Uganda: a cross-sectional diagnostic study. BMC Infect Dis. 2013;13:133.

114. Pilot project tests multi-drug resistant TB in children. Foundation for Innovative New Diagnostics; 2014 accessed 30 July 2014. (http://www.finddiagnostics.org/resource-centre/press/140430.html).

115. WHO Model list of essential medicines for children, 3rd list. Geneva: World Health Organization; March 2011.

116. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Geneva: World Health Organization; 2009 (http://www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf).

117. Prequalification of Medicines Programme. WHO list of prequalified medicinal products. World Health Organization; (http://apps.who.int/prequal, accessed 19 April 2013).

118. Survey of policy and practice in the treatment of pediatric TB in high burden countries. Geneva: TB Alliance and World Health Organization; 2014. Unpublished data.

119. Department of Health. Contract: HP02-2013AI: supply and delivery of anti-infective medicines (antibiotics, anti-fungal, antiprotozoal and anti-viral agents) to the Department of Health for the period 1 August 2013 to 31 July 2015. Pretoria: Republic of South Africa; 2013.

120. WHO list of prequalified medicines. Geneva: World Health Organization; 2014.

121. Lists of A,B and ERP-reviewed products. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2014 (http://www.theglobalfund.org/en/procurement/quality/pharmaceutical, accessed 29 July 2014).